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A RESEARCH UPON ANÆSTHESIA.

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INTRODUCTORY.

The subject of anæsthesia has been threshed over so thoroughly and so frequently by various investigators that at first sight it may appear hopeless to expect to find anything novel. Nevertheless, it has seemed to the writers of the present article that there are certain problems of importance which still remain to be solved. Although these problems have in many ways relations which are close to one another, and although they all have direct bearings upon one common theme —the use of anæsthetics—nevertheless they are sufficiently disjointed for each to be a special subject of research.

Moreover, in some cases such a research naturally leads the investigator somewhat far afield from the general problem of anæsthesia. It has, therefore, seemed wisest to divide the present memoir into distinct chapters. An introductory chapter like the present is, of course, the place in which the problems to be investigated should be stated.

The relations between the function of respiration and that of circulation are such that a suspension of either must of necessity be very shortly followed by a corresponding alteration of the other, but how far a mere lowering in the activity of one function is immediately

deleterious to the other still remains an open question. The effects of ether and of chloroform upon the circulation are so diverse that the relations between these effects and the respiration may in some cases become an important factor in determining a choice of the anæsthetic. The first chapter will therefore be devoted to answering the question: What effect has lessened blood supply to the brain upon the respiration and upon the vaso-motor system?

The depression of the arterial function is more pronounced during chloroformization than etherization; so that it seems but a natural conclusion that chloroform will leave the circulation more depressed than does ether; but as such conclusion may or may not be correct, the second chapter of the present research is devoted to the consideration of the question: Does the circulation recover itself more rapidly after prolonged deep etherization than after a similar narcosis produced by chloroform?

It is well known that occasionally persons who have passed through a prolonged anæsthesia, during which they have suffered severe surgical operation, die without obvious cause within a short period after the return of consciousness. In such case the doubt is whether the prolonged anæsthesia or the operation has been the cause of the death. As it is not possible by clinical observation to determine whether such a death as that just spoken of is or is not the result of the anæsthesia, and since it is plainly improper to experiment upon human beings, we have attempted in our third chapter to answer the question: Is it possible to have death produced by an anæsthetic some time after the cessation of its administration and the return of consciousness?

If it should be found that an anæsthetic may cause death after its more obvious effects have passed off, the question as to the reason for this death forcibly presents itself, but the consideration of this we shall defer for the present.

Early in the present research we found that a practical difficulty was the tendency of animals to die during a prolonged narcosis from an anæsthetic. As many of the experiments required hours for their performance, and as the time selected by the dogs for dying was usually when the experiment was nearly complete, it will be seen that

this difficulty caused much loss of time and annoyance. This led to the invention of a method of producing anæsthesia which we have used with much satisfaction.

We prepared a simple apparatus, consisting of a gallon glass jar, having a perforated india-rubber cork, through which ran two glass tubes, one short and one long, the latter reaching nearly to the bottom of the jar. Into the jar was put a small measure of the anæsthetic, and the short tube was then connected with a cannula in the trachea of the dog to be experimented upon. This not only enabled us to practice great economy in the use of the anæsthetic, but also, as soon as alarming symptoms appeared, to remove the anæsthetic and without loss of a moment connect the tracheal cannula with an apparatus for artificial respiration and forthwith restore the animal to life.

CHAPTER I.

What effect has lessened blood supply to the brain upon the respiration and upon the vaso-motor system?

The general idea of the method of research which we have employed in attempting to answer the question which heads this chapter has been to reduce the blood supply of the medulla oblongata by interference with the permeability of the arteries of the neck. In carrying out the method we have uniformly followed a very simple plan of experimentation. Under ether the carotids and the vertebral arteries have been first exposed low down in the neck and a ligature laid around them so loosely as not in the slightest degree to interfere with the blood flow. The effect of the anæsthetic has been allowed thoroughly to subside, and observations were then made upon the function (to be studied) in its normal state. After these observations have been completed, one, two, three or all of the arteries (according to the individual experiment determined upon) have been rapidly tied, and the effect upon the function under study has been noted. In some instances we have used tight clips instead of ligatures, so that by closing or opening the clips the flow of blood in the arteries of the brain could be arrested or allowed to go on at will.

The first series of observations related to the respiration. In these

the amount of air moved in the lungs was measured before and after the tying of the arteries, great care being taken as far as possible to have the animal free from any emotional excitement, so as to get an even balance of respiration and circulation both before and after the tying of the arteries. In every case the amount of air expired from the lungs was measured during five minutes, so that when a "period" is spoken of in the experiments, such period is always of five minutes duration.

In some of the animals the exposure of the four arteries produced excessive shock; in others, without injury to the pneumogastric nerve, marked Cheyne-Stokes respiration. As these phenomena developed before the tying of the arteries, the results were in nowise dependent upon arrest of the flow of blood to the brain; further, as the mere operation itself in these animals caused so much disturbance of respiration, the experiments were not carried to a final conclusion, or if this were done the results were altogether rejected in making up our account. Only when the animal became quiet, calm, free from excitement and apparently free from pain after the operation, were the experiments carried to full consummation and taken into consideration.

In making these experiments we have reached some very interesting collateral results which are worthy of note. Usually, tying the arteries has no immediate distinct effect upon a respiratory function, but we have noted that in certain dogs the respiratory centre seems to be thrown off its balance with extraordinary ease, and in this fact probably lies the explanation of certain anæsthetic deaths in which the respiration has been arrested unexpectedly by a moderate amount of the anæsthetic, or at a period in the anæsthesia when there is usually no danger. Thus, in a certain dog (A) respiratory arrest occurred early in an anæsthesia from ether. When it was evident that the arrested respiration could not be re-established by nature, and the heart was rapidly failing, artificial respiration was resorted to with the usual effect of resuscitation. Afterwards, when we tied the carotids (without anæsthesia at the moment), immediate lethal arrest of respiration took place, from which the animal was again resuscitated as before; and the same phenomena resulted when the vertebrals were

tied. In this dog, then, the respiratory centres were so abnormally susceptible that procedures which commonly do not disturb the functions of the centres produced a fatal paralysis. Careful post-mortem investigation of the animal failed to give, at least so far as macroscopic appearances were concerned, any explanation of this lack of robustness of the respiratory centres.

In the first series of experiments the carotid arteries alone were tied, and the effects noted. These experiments are as follows:

EXPERIMENT I.

Period.	Rate of Respiration.	Amount of air moved in cubic feet.	Remarks.
1	27	10.3	Much of the time struggling.
2	28	8.06	Struggling some of the time.
3	22	5.69	Very quiet the whole period.
4	22	6.32	Very quiet the whole period.
Both carotids tied.			
5	27	6.69	Very quiet the whole period.
6	27	6.81	Very quiet the whole period.

EXPERIMENT II.

Period.	Rate of Respiration.	Amount of air moved in cubic feet.	Remarks.
1	27	5.75	Very quiet.
2	28	4.47	Very quiet.
One carotid tied.			
3	29	6.12	Very quiet.
4	28	5.79	Very quiet.
5	26	6.40	Very quiet.
Second carotid tied.			
6	34	6.34	Very quiet.
7	36	6.87	Very quiet. Pupil widely dilated; reacts partially to light.
8	25	5.18	Very quiet.

In interpreting the foregoing experiments it must be remembered that there is a slight variation in the amount of air moved by the animal from period to period, even though there be perfect quiet and apparent freedom from emotional disturbance. It is plain that in Experiment I simultaneous tying of both carotids had no distinct effect upon the amount of air moved, since the difference between the last period (4) before tying and the period immediately after tying

(5) was about half the difference between periods 3 and 4 when the arteries were free.

An examination of Experiment II leads to confirmatory results. There was, to be sure, a slight apparent rise when the first carotid was tied (between periods 2 and 3), but period 4 immediately following period 3 was absolutely the same as period 1; whilst tying the second carotid had no distinct effect upon the air movement, which in period 8, about fifteen minutes after the second carotid had been secured, was a little less than in the first normal period.

These experiments seem to show that such lessening of the blood supply to the brain as is caused by tying simultaneously the carotids does not sensibly affect the respiratory function.

The next series of experiments was performed to determine the effect of arresting the circulation in the carotids immediately after the vertebral arteries had been tied.

EXPERIMENT IV.

Period.	Rate of Respiration.	Amount of air moved.	Remarks.
1	42	4.95	Very quiet.
2	39	4.63	Very quiet.
Tied both vertebrals and one carotid; put clip on other carotid immediately before next observation.			
3	24	3.76	Very quiet.
4	24	4.21	Pupils widely dilated; do not react to light.
Freed both carotids.			
5	22	2.95	Very quiet.
Tied both carotids.			
6	22	2.70	Very quiet.
7	28	2.95	
Dog allowed to walk about, did so with ease; reflexes, gait and station about normal, but pupils fixed in wide dilatation.			
8	18	3.65	Dog killed at end of observation.

EXPERIMENT VI.

Period.	Rate of Respiration.	Amount of air moved.	Remarks.
1	53	6.00	Struggled a little.
2	42	7.48	Struggled a little.
3	47	7.04	Struggled a little.
4	44	6.88	Quiet.

Tied vertebrals: two minutes later clipped both carotids: breathing immediately profoundly affected; became deep and labored, with pronounced failure of expiration, the animal being seemingly unable to empty the lungs, causing progressive distension of thorax and abdomen. Observation 5 begun less than one minute after putting on clip.

Period.	Rate of Respiration.	Amount of air moved.
5	12	1.4

Clip taken off, but respiration did not change in next four minutes when the carotids were tied. The animal taken off the table semi-conscious and unable to stand. Ten minutes after carotids were tied the animal died in spasm. At autopsy the nerves were found not injured; vessels all tied.

EXPERIMENT VII.

Period.	Rate of Respiration.	Amount of air moved.	Remarks.
1	43	5.00	Quiet.
2	57	6.01	Some struggling.
3	58	5.00	Quiet.
4	52	4.05	Quiet.
5	53	5.04	Quiet.
6	53	6.02	Slight struggling.
Vertebrals tied; carotids clipped: observation 1 minute later.			
7	50	4.05	Quiet.
8	44	6.00	Quiet.
9	50	4.77	Slight struggling.
10	41	3.47	Quiet.
11	34	3.16	Quiet.
Clips removed from carotids; next observation 1 minute later.			
12	36	5.07	
13	34	3.01	
14	34	3.04	
Clipped both carotids; observation began 1 minute later.			
15	34	3.06	
16	34	2.08	
Dog let up; conscious, able to walk, but very ataxic.			

EXPERIMENT VIII.

Period.	Rate of Respiration.	Amount of air moved.	Remarks.
1	34	7.67	Quiet.
2	32	4.72	Quiet.
3	31	4.88	Quiet.
Tied vertebrals; clipped carotids; observation began 2 minutes later.			
4	30	5.04	Quiet.
5	28	6.00	Quiet.
Clips taken off carotids; observation 2 minutes later.			
6	31	6.16	Quiet.
Clips put on carotids.			
7	30	6.95	
8	29	6.40	
Dog when let up walked fairly well, although somewhat ataxic.			

An examination of the record of Experiment IV shows that in the first period after the complete arrest of circulation in the arteries of the neck, there was an apparent very slight reduction in the air movement, with almost complete recovery in the second five minutes. After this, however, in spite of the removal of the clip from the carotids, the air movement very sensibly decreased and did not at any time before the killing of the animal come back to the norm.

In Experiment VI clipping of the carotids was followed by a pronounced alteration in the character of the respiration, and also by a very great fall in the air movement.

In Experiment VII arrest of the circulation was followed by immediate fall in the first period of the air movement, with complete recovery in the second period; and after that a steady, persistent lowering in the movement of air to the end of the experiment, a lowering which was at one time temporarily interrupted by removal of the clips from the carotids.

In Experiment VIII there was practically no difference in the air movement in period 3 (just before arrest of circulation) and in period 4 (just after); though subsequently there was a rise in the air movement, though not to the point of period 1.

The most discordant of these experiments in its results was Experiment VI; in it the arrest of circulation was followed by a nearly complete respiratory paralysis, the paralysis especially affecting the expiratory movement, which seemed to be almost arrested. On the opposite end of the pendulum swing is Experiment VIII, in which the clipping of the carotids seemed to increase rather than decrease respiratory air movement. It is worthy of remark that the dog in Experiment VI rapidly died, whilst the animal in Experiment VIII seemed very little affected by the operation.

The explanation of the comparatively little effect in the tying of the arteries must be, of course, found in the relief afforded to the animal by a collateral circulation, and it is probable that in the dog used in Experiment VI the collateral circulation was anatomically very little developed; whilst in Experiment VIII the arterial structure was such that the brain received a sufficient supply of blood to main-

tain it after all the carotid and vertebral arteries had been tied. The conclusion which it appears to us can be drawn from these experiments is, that the respiratory centres are remarkably insensitive to a lowering of their blood supply, and that when this movement is sufficient to produce any effect, such effect is functional, depression ending in paralysis with complete or nearly complete arrest of respiration after the arteries had been tied. In two cases we noted that section of the pneumogastric nerves was followed by an immediate permanent arrest of breathing, although in several other cases this arrest of breathing did not occur when the par vagum was severed. It would appear that an underfed respiratory centre is more dependent for its activity upon the impulses which reach it through the pneumogastric nerve than is the normal centre; or else that it is less able to resist the disturbance of a shock such as may be produced by section of the nerve.

CIRCULATION.

In order to determine the effect upon the circulation of tying the carotid and vertebral arteries we have made the following series of experiments. In each of these experiments the cannula was introduced into the left carotid, so that the first record was taken with one carotid artery already separated from the cerebral circulation.

EXPERIMENT VI.

Time.	Pulse 10 sec.	Pressure in mm. Hg.	Respiratory rate 30 sec.	Remarks.
4.12.20	23	90		
4.14	19	90		
4.15				Tied right vertebral.
4.15.10	22	90		
4.16	18	92		
4.17	17	100		
4.20	16	90		
4.20.40				Tied left vertebral.
4.20.50	15	88		
4.21	17	95		
4.31	14	64		
4.31.30	13	56		

In this experiment the effect of tying the one vertebral artery was an apparent slight rise in the arterial pressure; which rise seemed to

continue for a time after tying of the other artery, followed, however, after some minutes by a distinct fall.

In the following experiments both vertebrals were tied, and the carotids also were either tied or else their lumen obliterated by clipping. The left carotid was obliterated by insertion of the cannula.

EXPERIMENT VII.

Time.	Pulse 10 sec.	Pressure.	Respiratory rate 30 sec.	Remarks.
5.59	24	72	9	Reflexes good.
5.59.30				Tied left vertebral.
6.00				Tied right vertebral.
6.00.20	24	70		Tied right carotid.
6.00.40	25	76	14	
6.01	25	86		Shut off respiration mechanically.
6.01.30		80		
6.02		76		
6.02.30		80		
6.03		98		Struggling; corneal reflex present.
6.03.30	12	66		Efforts to breathe stopped.
6.04	11	66		Conjunctival reflex gone.
6.04.20		16		
6.06.30				Heart stopped.

EXPERIMENT X.

Time.	Pulse 10 sec.	Pressure.	Respiratory rate 30 sec.	Remarks.
4.44	28	108		
4.44.30				Right vertebral tied.
4.44.50				Left vertebral tied.
4.45	30	108		
4.45.50				Right carotid clipped.
4.46	30	102		
4.46.30				Struggling.
4.47	31	164		Quiet.
4.47.30	31	170		
4.48	29	156		
4.48.50				Clip off right carotid.
4.49	30	150		
4.49.30	28	144		Clip on right carotid.
4.50	27	164		
4.50.30	29	169		
4.51	28	168		
4.53	28	148		

EXPERIMENT XI.

Time.	Pulse 10 sec.	Pressure.	Respiratory rate 30 sec.	Remarks.
4.20	25	116		Breathing quietly.
4.20.20				Right vertebral tied.
4.20.50				Left vertebral tied.
4.21	24	116		
4.21.20				Clip on right carotid.
4.21.40	22	134		Artificial resp.
4.21.50				Clip off.
4.22	23	116		
4.22.10				Clip on.
4.22.30	23	130		
4.22.40				Clip off; artificial resp. off.
4.23	19	116		Feeble breathing.
4.23.30				Clip on. Resp. regular.
4.23.40	20	134		
4.23.50				Clip off.
4.24	19	118		

An examination of the records of the experiments just given shows that in Experiment VI the complete closing of the vertebrals and carotids was followed by a pronounced rise in the arterial pressure, amounting to 14 millimetres. In Experiment X the obliteration of one carotid and both vertebrals produced no appreciable effect upon the arterial pressure; but subsequent clipping of the right carotid was followed by a persistent rise of the pressure, so that in one minute and a half (the animal being quiet) the arterial pressure had increased from 108 to 170; further, the removal of the clip from the carotid was followed by a rapid and pronounced rise of pressure when the lumen of the carotid was again obliterated. In Experiment XI the results were a counterpart of the results of Experiment X; no effect was produced by tying the vertebral arteries, but each time the clip was put on and off the carotid there was a corresponding rise or fall of pressure.

These experiments, and others which we have performed of similar import, show that a sudden obliteration of the four arteries in the dog is usually followed by an immediate rise of the arterial pressure.

The question now suggests itself whether the rise of the arterial pressure just spoken of is due to a vaso-motor spasm; or whether it is simply the result of reducing the territory which is supplied by the

blood, with the consequent alteration of the relation between the volume of blood circulating and the size of the cavities or tubes in which it circulates; in order to test this we made the following experiment:

EXPERIMENT XII.

Stout dog. Spinal cord was cut at the sixth cervical vertebra, above the origin of the splanchnic nerve, and both vertebral arteries were tied. Artificial respiration was practiced at first, and when the animal had entirely recovered from the anæsthetic it was found that diaphragmatic breathing went on with sufficient force for practical purposes.

Time.	Pulse 10 sec.	Pressure.	Respiratory rate 30 sec.	Remarks.
5.13	30	56		
5.13.30	29	58		
5.14	30	58		Right carotid clipped.
5.14.40	30	59		
5.14.50				Clip off.
5.15	28	56		
5.15.30	29	56		
5.15.40				Clip on again.
5.16	30	58		
5.16.30	29	58		
5.16.30				Clip off.
5.17	26	56		
5.18	29	46		
5.18.30	25	48		
5.20.40	30	50		
5.20.50				Clip on again.
5.21	27	55		
5.21.30				Clip off.
5.21.40	32	52		
5.24.20	29	56		
5.24.30				Clip on carotid.
5.24.40	26	60		

An examination of the record of the experiment just given shows that after paralysis of the vaso-motor system by section of the cord, cutting off the only remaining artery going to the head in half a dozen trials was always followed by a slight rise in the arterial pressure; this rise of the arterial pressure being usually one or two millimetres, and in no case exceeding five millimetres. Contrasting this result with the result produced by closing the last artery in the normal dog, it is evident that though reduction of the territory supplied by blood may in these cases have a little influence in raising pressure, this

influence is only very slight and not at all sufficient to explain the rise following obliteration of the arteries in the normal animal.

The second factor acting in the production of the rise of pressure caused in the normal dog by tying the arteries in the neck is not far to seek; it must be a vaso-motor spasm of centric origin; so that the conclusion is reached that the great reduction in the blood supply to the medulla caused by tying the arteries in the neck evokes functional excitement of the vaso-motor centres in the medulla, and consequent contraction of the blood-paths with rise of the arterial pressure. The stimulating effect of withdrawal of the blood upon the vaso-motor centres is not, however, equal to that which is produced by asphyxia. This can readily be seen by comparing the amount of rise in the experiments which we have detailed with that which habitually occurs in the normal dog during asphyxia. Moreover, in several experiments, which it does not seem necessary to record here in detail, we found after tying the arteries and getting the increase of arterial pressure, asphyxia was still able to cause a distinct further rise.

PNEUMOGASTRICS.

In the course of our experimentation we have made some studies to determine whether tying the arteries had a perceptible influence upon the cardiac centres or fibres of the pneumogastric nerves; our results have been somewhat doubtful. Thus, in Experiment XI the pulse was 24 to ten seconds, fell to 22 when the artery was clipped, rose to 23 when the clip was taken off, remained unchanged when the clip was put on, fell to 19 when the clip was off, rose to 20 when the clip was put on, fell to 19 again when the clip was off, then rose to 32, the arteries being free, falling to 30 when the carotid was clipped, and ranging, when the two vagi were cut, directly upwards from 30 to 35.

It seems to us plain that tying the vertebrals and carotids has no overpowering action upon the cardiac pneumogastric centres.

The outcome of the research which we have thus reported has been to us somewhat surprising in the little immediate effect which has been produced by simultaneously tying all four of the cerebral arteries. In all our experiments the vertebral arteries were always tied low

down in the neck; the carotids were sometimes tied very low down, but were more usually ligatured a little below the level of the lower edge of the larynx. To determine whether there are any after-effects from ligating the arteries, a large dog was operated upon antiseptically. The recovery took place without difficulty, and at no time during some subsequent weeks could there be noted anything abnormal in the intellectual functions of the dog, unless it were his excessive activity and energy; but the pupils remained after the operation wide spread, their power of responding to light having been almost entirely lost; so that in a very bright light there was a manifest photophobia in the animal, evidently due to the inability to contract the pupil.

The explanation of the little effect produced by tying the arteries must of course be the existence of a collateral circulation whose potential activity we at least had not previously suspected. To test the matter further Dr. J. P. Arnold made several further experiments. In one of these experiments the head was trephined two weeks after the arteries had been secured, and the cerebral pulsation was seen to be marked, although less active and pronounced than in the normal dog. In three dogs killed from two to six weeks after tying the arteries, and subsequently injected through the aorta, the carotids and vertebrals were found empty above the points of ligation. The superior intercostals and their deep cervical branches were considerably enlarged. The basilar artery and the circle of Willis were empty. There was no sign of any of the injection having entered into any of the vessels of the brain.

It would seem in conclusion that the collateral circulation after tying the neck arteries is rapidly established; partly through the enlargement of the superior intercostals and their deep cervical branches, which anastomose with the deep cervical branches of the occipital from the external carotid, and partly through the branches of the superior intercostals to the spinal cord, which anastomose with the descending spinal branches of the vertebral. The fact that the injecting fluids invariably failed to reach the brain shows that during life the brain must have been supplied with blood through numerous minute vessels, rather than through several large ones.

CHAPTER II.

Does the circulation recover itself more rapidly after prolonged deep etherization than after a similar narcosis produced by chloroform?

In order to answer the question which heads the present chapter we have made two series of experiments. In the one series two dogs were selected, as nearly alike as might be; the normal arterial pressure taken in the carotids, and then to one dog ether, to the other chloroform was given. In each case, after narcosis had been maintained for a certain period, the anæsthetic was withdrawn and the arterial pressure taken as soon as consciousness was restored. In some experiments the dogs were then again narcotized and the pressure again taken upon the recovery of consciousness. In every case finally the narcosis was allowed to pass off and the pressure taken twenty minutes after the return of full consciousness.

In the second series of experiments, instead of two dogs being employed for the one experiment, the same dog was used twice. One narcotic was given, the records taken as in the previous series of experiments, and then the dog put back into the kennels and taken care of until fully recovered. The alternate narcotic was then administered and the record taken as before. In all these cases the anæsthetic was administered by means of the apparatus which we have previously described. The operation was done antiseptically, and the wound healed in each case rapidly and without evidence of serious illness. Nevertheless, since it is conceivable that the traumatism and the confinement in the kennels, as well as the first narcosis, might produce some weakening of the animal, and probably render somewhat unfair a comparison of the two records obtained, the experiments were balanced one against the other. Thus in the first experiment chloroform was used for the first narcosis, ether for the second; in the second experiment ether was first used, chloroform second; in the third experiment chloroform was first used and ether second; and in the last experiment ether was first used, afterwards chloroform. It is plain that when the average of these experiments is taken the sources of fallacy just spoken of are eliminated.

The experiments are as follows: It must be noted in reading them that the word "Norm" at the head of the first column means the pressure taken before the administration of anæsthetic; that in the second, and sometimes third, columns the time given is the duration of the narcosis, the record showing the arterial pressure taken as soon as the narcosis had gone off sufficiently for the recovery of consciousness. The last column gives the arterial pressure twenty minutes after the complete recovery of consciousness.

FIRST SERIES.

Experiments with Two Dogs.

	Norm.	Duration of inhalation 60 min. Record immediately after recovery.		20 minutes after consciousness.
Ether.....	140	114		118
Chloroform	134	108		122
		60 min.	Duration of inhalation.	
Ether.....	140	140	117 (120 min.)	126
Chloroform	100	84	72 (90 min.)	88
		90 min.		
Ether.....	145	126		134
Chloroform	130	108		98
		60 min.	90 min.	
Ether.....	134	100	120	123
Chloroform	126	136	120	122

SECOND SERIES.

Experiments with One Dog.

	Norm.	Duration of inhalation 60 min.	Duration of inhalation 90 min.	20 minutes after consciousness.
Chloroform	100	84	72	88
Ether.....	134	100	92	
2nd dog two weeks after first observation.				
		90 min.		
Ether.....	145	126		134
Chloroform	160	130		114
2nd dog four weeks after first observation.				
		60 min.	90 min.	
Chloroform	126	130	120	122
Ether.....	148	136	128	
		60 min.	90 min.	
Ether.....	134	100	120	123
Chloroform	148	145	122	137

An examination of the above record of our experiments will show that so far as the circulation is concerned the degree of recovery from the effects of the anæsthetic in the periods named does not differ very materially whether chloroform or ether has been employed, although there is a distinct advantage on the side of chloroform. To show this more clearly we have thrown the results in the form of two tables. In the first of these tables is exhibited the difference between the norm and the arterial pressure after the 60-minute period (or the 90-minute period in one or two experiments); and in the second table are placed the differences between the norm and the arterial pressure 20 minutes after the return of consciousness.

TABLE 1.

	FIRST SERIES OF EXPERIMENTS.		SECOND SERIES OF EXPERIMENTS.	
	Ether.	Chloroform.	Ether.	Chloroform.
	26	26	34	16
	..	16	9	30
	19	22	12	4
	34	10	34	3
Average	17.25	13.5	22.25	11.25

TABLE 2.

	FIRST SERIES OF EXPERIMENTS.		SECOND SERIES OF EXPERIMENTS.	
	Ether.	Chloroform.	Ether.	Chloroform.
	22	12	34	12
	14	12	11	46
	11	32	20	4
	11	4	11	11
Average	17	15	19	18.25

When we compare the average fall of pressure of the two anæsthetics we note that in Table 1 in the first series of experiments the average is 17.25 after ether, 13.5 after chloroform; in the second series of experiments it is 22.25 after ether and 11.25 after chloroform. The result here is very distinctly and decidedly in favor of chloroform. In Table 2 it will be noted that in the first series of experiments the average after ether is 17, after chloroform 15; in the second series of experiments, after ether 19, and after chloroform 18.25.

The question of the rebound of the vascular system from the anæsthetic would seem to be connected with the ease with which the drug is eliminated from the system. Chloroform being in smaller quantity than the ether, and also more volatile, is evidently thrown off more rapidly than the ether; hence a very few minutes after the withdrawal of the anæsthetic the recovery from chloroform, as shown by the tables, is greater than from ether; but later, when twenty minutes were allowed to elapse, the elimination of the ether had evidently progressed far enough to allow the circulation to regain nearly its original force.

CHAPTER III.

Is it possible to have death produced by an anæsthetic some time after the cessation of its administration and the return of consciousness?

The history of prolonged anæsthesia, even when accompanied by great surgical operation, shows that death from shock or from any other mysterious cause shortly after the return of the patient to consciousness is a very rare phenomenon. It cannot, therefore, be expected that in the lower animals a prolonged anæsthesia should be often followed by death. Further, it must be noted that the question which heads the present chapter refers not only to the normal but also to the diseased animal. Especially is this wide significance necessary in view of the fact that the anæsthetic often has to be used even though the human individual is the subject of organic disease. These considerations lend importance to the two experiments we have to report, in which no other apparent cause of death than the after-effects of the anæsthesia existed. The surgical procedures consisted simply in putting a cannula in the carotid artery and in re-opening the trachea through the wound made ten days before. There could have been no surgical shock, there was not the loss of a teaspoonful of blood. The experiments are as follows:

EXPERIMENT I.

A large shepherd dog, which ten days before had been subjected to deep chloroformization for over an hour and a half. The pressure before the commencement of etherization was 160. Etherization was continued for one and a half hours, at the end of which time the pressure

had fallen to 140. Five minutes after the withdrawal of the ether consciousness was complete, and the pressure had risen to 160. Although no more ether was given, five minutes later the pressure spontaneously had fallen to 150, and there was some irregularity of respiration; ten minutes later the pressure was 130 and the respiration markedly irregular. Unfortunately it so happened that at this point the tracing paper was full and no further tracing was taken; but the arterial pressure slowly fell, the respiration became more and more irregular; and five minutes after the last observation, that is twenty-five minutes after the withdrawal of the ether, respiration ceased entirely, the cessation being rapidly followed by arrest of the heart.

EXPERIMENT II.

Black-and-tan terrier. Had been etherized about ten days before for nearly two hours. Arterial pressure before present anæsthetic, 130. Was chloroformized for twenty minutes; two minutes after the return of consciousness the arterial pressure was 82; fifteen minutes later the arterial pressure was 62, and respiration at this time was regular. From this time the pressure began to fall rapidly, and the dog died twenty-seven minutes after the withdrawal of the chloroform.

These two experiments seemed to us positively to prove that a dog may die from the effects either of prolonged chloroformization or of prolonged etherization at least half an hour after the recovery of consciousness; this, too, in cases in which at the time at which consciousness first comes back there are no symptoms presaging an evil result. Later experiments, not here reported in detail, have abundantly confirmed these conclusions. If such a result can occur in the dog, its happening is to be expected in human beings. It is certain that occasionally after severe surgical operation under prolonged anæsthesia death does occur in man within a short period after the recovery of consciousness; the cause of the death being very obscure, no grave lesions being found in the body to account for the fatal result, which has been attributed by most surgeons to an indefinite something called "shock." In view, however, of the positive experimental results which have been reached, it seems to us that it must be considered an established proposition that death from an anæsthetic may occur in a human being after the loss of consciousness and the characteristic obvious effects of the anæsthetic have passed off.

CONCLUSIONS.

The conclusions which have been reached by the series of experiments recorded in the present memoir are:

First. Lowered arterial pressure has a comparatively feeble effect upon the respiration, but when the pressure falls sufficiently, respiratory depression does occur.

Second. Even excessive lowering of blood pressure primarily stimulates the vaso-motor centre, the sensibility of the centre being evidently necessary to the automatic regulation of the circulation.

Third. The circulation recovers itself more slowly after profound etherization than after a like chloroform narcosis.

Fourth. It is possible for ether as well as chloroform to produce death some hours after the cessation of its administration, at a time when the cerebrum has long freed itself from distinct evidences of the narcotic, so that consciousness and intellectual action have been restored.

In applying these conclusions to the subject of practical anæsthesia it is evident that the depression of the circulation produced by chloroform has effect upon the respiratory centres only when the pressure has fallen very low, and whilst it may be a factor in the production of respiratory failure during chloroformization, the failure must be chiefly due to the direct influence exercised by the drug upon the respiratory centres.

Clinical experience shows that nausea and general depression are more pronounced after the use of ether than after the use of chloroform, a difference which is strongly insisted upon by the advocates of chloroform as an important agent in favor of that anæsthetic. Our research confirms clinical observation, and experimentally shows that the depression of the circulation produced by ether is more permanent than that caused by chloroform; the reason probably being the large amount of ether which is necessary to produce profound narcosis, with lowering of the arterial pressure; an amount so large that it can neither be burned up in the system nor yet eliminated in the time which would be necessary for the much smaller amount of chloroform to be gotten rid of after chloroformization.

EXPERIMENTS ON THE RELATION OF THE INHIBITORY TO THE ACCELERATOR NERVES OF THE HEART.

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Part I.

INTRODUCTION.

The conclusions reached by Baxt* from his experiments upon the relation of the vagus to the accelerator nerves of the heart, published about twenty years ago, seem to have been very generally accepted. He states in this work that when the two nerves are stimulated simultaneously, the result during the stimulation is the same as when the vagus alone is stimulated, and that this is true even when the vagus is stimulated with a minimal and the accelerators with a maximal stimulus.

A few experiments have been published which indicate that this view of Baxt is not tenable. Thus Bowditch,† whose work preceded and suggested that of Baxt, stated that in his experiments in which the two nerves were stimulated simultaneously the accelerator overcame the inhibitory nerves as frequently as the latter did the former, and very similar results had been obtained by Schmiedeberg‡ still earlier; Bayliss and Starling§ showed that when the auricles had been slowed or brought to a standstill by stimulation of the vagus, the ventricles could be made to beat more rapidly by stimulating the accelerators; and Meltzer,|| after a careful examination of Baxt's tables, expresses the opinion that the conclusion just the opposite to that reached by Baxt is to be drawn from them, viz., that when the

* Baxt, *Arbeiten aus der physiolog. Anstalt zu Leipzig*, 1875, p. 179.
† Bowditch, *Arbeiten aus der physiolog. Anstalt zu Leipzig*, 1873, p. 259.
‡ Schmiedeberg, ibid., 1871, p. 34.
§ Bayliss and Starling, *Journal of Physiology*, xiii, p. 414, 1892.
|| Meltzer, *Arch. f. Anat. u. Physiol.*, physiol. Abth., 1892, p. 376.

nerves are stimulated simultaneously the effect of the accelerators is seen during as well as after the stimulation. Meltzer also calls attention to the fact that a stimulation of the vagus arising in the centre in the medulla can be overcome by the accelerators, since stimulation of these causes an acceleration when the vagi are intact and in tonic activity.*

An examination of Baxt's tables, moreover, shows that in many cases at least the stimuli which he employed for the two nerves were not at all comparable with each other as regards their strength, if we take their effect upon the heart as the measure, which is evidently the only practicable method. Thus his first table shows that the stimulus applied to the vagus, instead of being a minimal one, was sufficiently strong to cause a slowing of the heart of from forty-four to ninety-one per cent; in most cases the figures were nearer the latter than the former number. On the other hand, the stimulus applied to the accelerators in this series caused in one case an acceleration of thirty-nine per cent; as a rule the acceleration was much less. When the stimuli used for the two nerves differed so widely in their relative strengths we should naturally expect the inhibitory effect to predominate, and the results certainly cannot be regarded as showing that a "minimal stimulation of the vagus can overcome a maximal stimulation of the accelerators."

Still the conception of Baxt that these nerves are not real antagonists, but that a stimulation of the vagus, whatever its strength, will overcome the accelerators even when these are stimulated to a maximum, seems to be the prevailing one,† and has served as the basis for speculations as to the manner in which these nerves affect the heart.‡

* Since the completion of this paper Dr. Hough has told me of some experiments bearing upon this subject which he performed some time ago, but the results of which he has not published; he produced standstill of the heart by stimulating the vagus, and during the "escape" of the heart from this standstill (the stimulation of the vagus being continued) the accelerators were stimulated and a marked acceleration resulted.

† See, for example, Stewart, *Journal of Physiology*, xiii, p. 114, 1892, and Engelmann, *Pflüger's Archiv*, lxv, p. 163, 1896.

‡ Tigerstedt, Lehrbuch der Physiologie des Kreislaufes, p. 271. Leipzig, 1893.

I am convinced from the experiments described in this paper that such a view is not tenable; that as far as the ventricle is concerned (and this was the only part of the heart investigated in these, as was also the case in Baxt's experiments) these nerves do act as pure antagonists to all stimuli which can be fairly compared with each other as regards their strength, and the reason that their true relation is often concealed is readily accounted for by supposing the inhibitory apparatus to be more irritable than the accelerator, just as Rutherford showed that the laryngeal muscles respond to a weaker stimulus of the vagus than does the heart.

Before describing the experiments it may be added, in order that the problem under discussion may be kept clearly in view, that they relate almost exclusively to the effects of stimulating the nerves for short periods of time only, *i. e.*, for periods too short for the results to be complicated by the fatigue of the accelerator mechanism. This was the case in Baxt's experiments also; but in these the duration of the stimulation was often so brief that, as Meltzer points out, we cannot be sure that sufficient time was allowed for the full development of the effect of the accelerators, which are known to have a very variable and often quite long latent period. The effect of stimulating the two nerves together for a very long period is, to a large extent, a different problem from that discussed in this paper; a few experiments bearing upon it, however, will be described in the latter part.

The results of the experiments will be described under three heads: (1) the effect of stimulating the vagus alone, (2) the effect of stimulating the accelerators alone, and (3) the effect of stimulating the two nerves simultaneously. Under the first two heads some points relating to the physiology of these nerves which have been observed incidentally will be described.

The general method of experimenting was the same in all cases. The animals employed were dogs, cat and rabbits, which were always thoroughly anæsthetized in some manner. The heart rate and blood pressure were recorded by a mercury manometer in the usual manner. The currents to the induction coils used for stimulating the nerves were supplied by large storage cells, so that there was little danger of

the current becoming perceptibly weaker during the course of an experiment. Other details as to the technique will be given in the proper place.

Part II.

STIMULATION OF THE VAGUS.

Method. — When the effect of stimulating the vagus alone is to be compared with that produced when the accelerators are stimulated at the same time, it is obviously necessary to use some form of stimulation which will give uniform and constant results. This requirement is difficult to meet in the case of the vagus, especially as we must often deal with minimal or almost minimal stimuli. Both Bowditch and Baxt call attention to the inconstancy of the results obtained by stimulating the vagus with the ordinary induced current. It seemed probable that a current the efficiency of which could be governed by the number of interruptions of the primary circuit as well as by the position of the secondary coil, could be made to give more constant results and at the same time admit of finer gradations. To obtain such a current the primary circuit of an ordinary Du Bois-Reymond induction coil was interrupted by an " oscillating rod " kept in vibration by an electro-magnet, the number of interruptions per second being determined by the length of the rod set into vibration. The vibrations were recorded upon a drum kymograph by means of a Desprez signal; a pen marking seconds wrote directly beneath this, so that the rate of vibration could be read off at any time. Three to nine double vibrations per second were found sufficient as a rule. By altering the number of interruptions of the primary circuit and changing the position of the secondary coil, the desired effect upon the heart could be produced when the vagus was stimulated; and it was found that this effect remained very constant during a number of succeeding stimulations as well as during a long-continued stimulation of the vagus. Numerous examples of the effect of stimulating the vagus in this manner for short periods (ten to fifteen seconds) will be given later; here the results of a stimulation continuing for some time will be described.

Effect upon the heart of a long-continued stimulation of the vagus with the slowly interrupted current.—During the course of a more or

less prolonged stimulation of the vagus in this manner slight changes in the rate of the heart occurred; the most common of these was a slight escape soon after the beginning of the stimulation. Hough* has recently described such an escape when the heart was slowed slightly by stimulating the vagus with the ordinary rapidly interrupted current. Judging from Hough's account, I think the escape occurs less frequently and is less complete when the slowly interrupted current is used; indeed, in some cases no escape whatever occurred, and in others, sometimes with, sometimes without a slight escape at the beginning, the rate of the heart decreased slightly but regularly as the stimulation continued. The following experiments will illustrate these points.

1. Cat. Ether anæsthesia. Vagi and accelerators cut. Peripheral end of l. vagus stimulated by current interrupted nearly 4 times per second; secondary coil 12 cm.

Time.			Heart-beats in 10 seconds.	Blood-pressure.	
hr.	min.	sec.			
3	53	50	40	107 mm.	
	54		30½	90+	Stimulus on vagus.
		10	28+	83+	
		20	28+	77	
		30	28½+	74	
		40	29−	71+	
		50	29	68	
	55		30½	64+	
	56		32½	65+	
	57		32	65	
	58		32	64	
4	1				Stimulus off vagus.
4	1	10	40½	99	

2. Cat. Ether. Vagi and accelerators cut. L. vagus; 4 interruptions per second; secondary coil 9 cm.

hr.	min.	sec.	Heart-beats in 10 seconds.	
3	30	30	19½	
		40	17	Stimulus on vagus.
		50	14+	
	31		15−	
		10	15	
		20	15+	
	32		15+	
	33		15½−	

* Hough, *Journal of Physiology*, xviii, p. 161, 1895.

The above experiments have been selected especially to illustrate the fact that the heart escapes from weak stimulation of the vagus after section of the accelerators.

3. Bitch. Morphine and ether, curare. Vagi cut; accelerators intact. R. vagus; $5\frac{2}{3}$ interruptions of primary circuit per second; secondary coil 0 cm.

hr.	min.	sec.	Heart-beats in 10 seconds.	Blood-pressure.	
2	24	40	50	70 mm.	
		50	33+	67	**Stimulus on vagus.**
	25		32+	63+	
		10	33+	63+	
		20	35½	63	
	26		35½	60	
		30	35½	59+	
		40	45½	67	**Stimulus off vagus.**
	27		49½	69	

The accelerators were now cut and the vagus again stimulated with the same strength of current.

hr.	min.	sec.	Heart-beats in 10 seconds.	Blood-pressure.	
2	46	10	32½	56 mm.	
		20	22	44	**Stimulus on vagus.**
		30	20½+	41	
		40	20½−	38	
		50	20½−	37	
	47		20½−	37	
	48		20½−	39	
	49		20−	41	
	50		19½−	42	
	51		18+	43	
	52		18−	43	
	56	10	35+		**Stimulus off vagus.**

The second of the foregoing tables illustrates the gradual slowing of the heart which sometimes occurs during the course of a prolonged stimulation of the vagus; such results, as well as the entire absence of escape, have been observed most frequently after section of the accelerator nerves, but not exclusively then, as the following shows.

4. Rabbit. Morphine and chloral. Vagi cut. Accelerators intact. L. vagus stimulated; secondary coil at 20 cm.; about $4\frac{1}{2}$ interruptions of the primary circuit per second.

hr.	min.	sec.	Heart-beats in 10 seconds.	Blood-pressure.	
4	2	30	28½−	51 mm.	
		40	26+	48	Stimulus on vagus.
		50	25+	48	
	3		25+	48	
		30	25+	48	
	4		25	48	
	5		25−	48	
	6		24+	48	
	7		23½	48	
	8		23	48	
	10		23	48	
	12		23	48	
	14		23	48	
	16		22½	48	
	17		21½	47	
	18	10	24+	48	Stimulus off vagus.
	19		26−	50	

Another point of interest in this connection is the fact that when the vagus is stimulated in the course of a prolonged stimulation of the accelerators, the heart escapes just as when the vagus is stimulated alone; an experiment illustrating this will be described in the latter part of this paper.

Effect of section of the accelerators upon the result of stimulating the vagus.—My experiments have not been sufficiently numerous or the results sufficiently constant to admit of very positive statements upon this point. In addition to the fact noted above that in general the escape of the heart from slowing produced by stimulation of the vagus seems to be less complete after section of the accelerators, the effect of the stimulation seems to be greater, as described long ago by Sustschinsky.* Thus in the above-quoted experiment upon the dog the maximum slowing before section of the accelerators was 36 per cent; after their section it was 50.7 per cent, when the same strength of current was used. No special attention, however, has been given to this point. Reflex stimulation of the vagus is much more effective after section of the accelerators; this point, however, will be discussed in a later paper.

* Sustschinsky, *Unters. aus dem physiol. Laborat. in Würzburg*, iii, p. 164, 1868.

Part III.

Stimulation of the Accelerator Nerves.

Effect upon the heart rate of cutting the accelerators.—In most of my experiments all the nerves going to the stellate ganglia, except the ventral limb of the annulus of Vieussens, were cut; this gave an opportunity of making observations upon the question of the tonic activity of the accelerator nerves, the evidence for which seems to be accumulating.* The ganglia were thoroughly exposed by opening the thorax and resecting the first ribs some time before the nerves were cut. With the ganglia thus exposed, it was very easy to cut all their connections without doing any injury to surrounding parts, so that the possibility of causing a reflex slowing of the heart through the vagi, in case these were not cut, was much diminished. In almost every case removal of the stellate ganglia caused a considerable decrease in the heart rate whether the vagi were cut or were intact. This is well shown in the experiment upon the dog already quoted (p. 156).

hr.	min.	Heart-beats in 10 seconds.	Blood-pressure.
2	28	49	71 mm.
	29	**R. stellate ganglion cut out.**	
	30	41+	66
	40	**L. stellate ganglion cut out.**	
	43	33	52

A point of interest not well shown in the above experiment is the difference almost always observed in the result of removing the right and left ganglia. In almost every experiment removal of the right ganglion caused a considerable slowing of the heart with little effect upon the blood pressure, while removal of the left had less effect upon the heart rate and more effect upon the blood pressure. This occurred whichever ganglion was removed first, and whether the vagi were cut or intact. A rather extreme case is the following:

* Timofeew, *Centralblatt f. Physiologie*, 1889, p. 235. Stricker and Wagner, *Wien. medizinische Jahrbücher*, 1878, p. 370.

Dog. Morphine and ether. Vagi intact.

hr.	min.	sec.	Heart-rate in 10 seconds.	Blood-pressure.
1	20		32½	108 mm.
	25		R. stellate ganglion cut out.	
	25	10	31	
		20	30+	
		30	30−	
		40	29	
		50	28−	
	26		26+	
		10	24+	
		20	24−	
		30	23½	
		40	23	
		50	22½	
	28		22	103
2	4		18	103
	6		L. stellate ganglion cut out.	
	8		18−	60

It will be shown in the next section that stimulation of the right annulus of Vieussens in these cases had a much more marked effect in accelerating the heart than did that of the left; this fact taken with the above seems to indicate that more accelerator fibres pass from the right stellate ganglion than from the left.

Similar results were obtained with cats, as is shown in the following:

Cat. Ether. R. vagus cut.

hr.	min.	Heart-beats in 10 seconds.	Blood-pressure.
11	51	37	106 mm.
	53	L. stellate ganglion extirpated	
	55	36	98
12	24	35	114
	26	R. stellate ganglion extirpated.	
	29	28+	109

Such experiments would seem to indicate that the accelerator centre is in tonic activity, but the possibility that the centre had been stimulated in some manner, as, *e. g.*, by the anæsthetics used—morphine and ether in the case of the dog, ether in the case of the cat—(just as morphine is known to stimulate the cardio-inhibitory centre*) must be remembered. In fact the excessively rapid heart often observed

* Gscheidlen, *Unters. aus dem physiol. Laborat. in Würzburg*, iii, p. 15. 1868.

after section of the vagi in dogs under the influence of morphine is very suggestive of such an action on the part of this drug, but I know of no experiments bearing upon this point. On the other hand this result, viz., slowing of the heart after section of the accelerators, has been observed under such various conditions and when no drug had been used (*e. g.*, when anæsthesia was produced by section of the crura cerebri) that I am inclined to accept the view that the accelerator centre is usually in tonic activity. In a few experiments it was impossible to cause, by stimulation of the accelerators, a greater frequency of the heart beat than existed before section of these nerves; apparently in such cases the accelerators had been in a state of maximal activity when they were cut.

One thing is certain, the slowing of the heart following section of the accelerators in these experiments cannot be referred to a reflex action through the vagus, for it occurred as often in animals in which the vagi had been cut or had been paralyzed by atropine as in those in which the vagi were intact; indeed it occurred more frequently in those in which the vagi were cut, a fact which I think can be explained by the following observation: All my experiments go to show that in properly anæsthetized animals, operative procedures tend to cause a diminution of the tonic activity of the cardio-inhibitory centre rather than to increase it. This is especially marked in dogs under the influence of morphine, upon which so many of my experiments were performed; in such animals I have repeatedly observed an increase of the heart rate, continuing often for several minutes, to follow such an operation as cutting the sciatic nerve, and as this has occurred in animals in which the stellate ganglia were completely removed, it can be explained only by supposing the tonic activity of the vagus centre to have been diminished. What appears to be a similar thing occurred in a few of my experiments upon the accelerators; thus in one the vagi were intact and the heart was beating at the rate of 43 beats in 15 seconds; the extirpation of the stellate ganglia caused an increase in the heart rate of 9 beats in 15 seconds, and this rate was but slightly increased by the subsequent division of the vagi.

The manner in which the slowing following section of the accelera-

tors occurred is interesting; it did not occur immediately upon section of the nerves, but developed gradually in the course of a period varying from one to several minutes. In other words the slowing of the heart from section of the accelerators is strikingly like the return of the heart rate to the normal after stimulation of these nerves. The second of the experiments described above illustrates this point very well.

Stimulation of the accelerators.—The accelerator nerves were stimulated in various parts of their course. In the dog those fibres running in the ventral limb of the annulus of Vieussens were usually stimulated; at times, however, the stimulus was applied to the rami communicantes passing to the stellate ganglion or to the small nerves given off from the annulus or the inferior cervical ganglion. In the cat the "nervus accelerans," as described by Boehm,* was stimulated.

There was seldom any difficulty in obtaining a marked acceleration of the heart when any of the above nerves was stimulated on the right side. The percentage of acceleration varied greatly in different experiments; the maximum effect I observed was an increase from 16 to 32 beats in 10 seconds, or an acceleration of 100 per cent.

Stimulation of these nerves on the left side in both dogs and cats has almost always in my experiments been much less effective than that of the nerves on the right side. Thus in the experiment recorded on page 159, stimulation of the right annulus caused an increase in the heart rate from 19 to 30 beats in 10 seconds, or an acceleration of nearly 58 per cent, while stimulation of the left annulus and of the rami communicantes passing to the left stellate ganglion caused a slight rise of blood pressure, but no change in the heart rate.

Occasionally a slowing of the heart, sometimes with, sometimes without a succeeding acceleration, resulted from the stimulation of the annulus; this occurred especially frequently when the left annulus was the one stimulated. Roy and Adami† describe results similar to these and suggest that they may be due to the stimulation of vasoconstrictor nerves of the coronary vessels. In some of my experi-

* Boehm, *Arch. f. exp. Pathol. u. Pharmakol.*, iv, p. 256, 1875.

† Roy and Adami, *Phil. Trans.*, clxxxiii B, p. 294, 1892.

ments this slowing was evidently a reflex effect through the vagi, for it could no longer be obtained when the vagi were cut. That afferent nerves may pass through the ventral branch of the annulus (especially on the left side) is shown by the fact that when this is stimulated, reflex movements of the legs and of the respiratory muscles sometimes occur; section of the vagi prevents the recurrence of these reflexes.

Stimulation of the accelerators after section of the vagi.—Since the vagi are usually in tonic activity, especially in dogs, we should expect to find the maximum to which the heart can be accelerated by weak stimulation of the accelerators to be greater after section of the vagi than before, that is if we assume that the two nerves are antagonistic. A few of my experiments indicate that this is the case, and I think it not improbable that the reason the others do not is due to the fact that the stimulus used was sufficiently strong to overcome completely the action of the vagi, and consequently the maximum rate was the same before as after section of the vagi. The "after-effect" of the stimulation of the accelerators, however, is markedly prolonged by the section of the vagi.

Since section of the vagi causes an increase in the heart rate, the percentage of acceleration from stimulating the accelerators is less after than before the vagi are cut. Still in such cases I have found no difficulty in obtaining an acceleration varying from 10 to 63 per cent. An acceleration has also been obtained after the administration of atropine till stimulation of the peripheral end of the vagus no longer caused a slowing of the heart.

Such experiments as the above corroborate the results of others, and show how incorrect is the statement, recently made,* that after section of the vagi or the administration of atropine no increase in the heart rate can be caused by stimulation of the accelerators.

* Roy and Adami, *op. cit.*, pp. 267 and 296. These authors describe, nevertheless (p. 246), an experiment in which stimulation of the left annulus caused an increase in the heart rate from 17 to 24½ beats in 10 seconds, after the vagus had been completely paralyzed by atropine.

PART IV.

SIMULTANEOUS STIMULATION OF THE VAGUS AND THE ACCELERATORS.

The results of these experiments will be described under three heads: (1) stimulation of the accelerators during a prolonged stimulation of the vagus, (2) stimulation of the vagus during a prolonged stimulation of the accelerators, and (3) stimulation of the two nerves begun at the same time.

1.

Stimulation of the Accelerators during a Prolonged Stimulation of the Vagus.

This phase of the subject does not seem to have been considered by Baxt. Bearing in mind, however, the great uniformity of the results obtained in a long-continued stimulation of the vagus, this method seems especially adapted to the solution of the problem of the relation of the two nerves.

The following experiment is a good illustration of what has invariably occurred:

Dog. Morphine and ether; curare. Vagi and accelerators cut. R. vagus stimulated; secondary coil at 0 cm.; primary circuit interrupted 5¾ times per second. R. annulus stimulated; secondary coil 10 cm.

hr.	min.	sec.	Heart-beats in 15 seconds.	Remarks.
2	46		49½	
		15		**Stimulation of vagus begun.**
	47		31½−	
	51		27+	**Maximal slowing 43.2%.**
	52		28	
		15	58	**R. annulus stimulated for 15 seconds.**
		30	58½	**Acceleration of 108.9%, or 18.1% above the normal rate.**
		45	44½	
	53		40½	
	56		39−	**Stimulus off vagus.**
		30	54½	

The stimulus was taken off the vagus while the after-effect of the stimulation of the accelerators was still evident.

The accelerators were now stimulated alone with the same strength of current as was used in the above. The results were as follows:

hr.	min.	sec.	Heart-beats in 15 seconds.	Remarks.
2	58	30	53+	
		45	75½	R. annulus stimulated for 15 seconds.
	59		77	Acceleration of 45.3%.
3			63	
	2		60	

These results are shown in the plotted curves in Fig. 1.

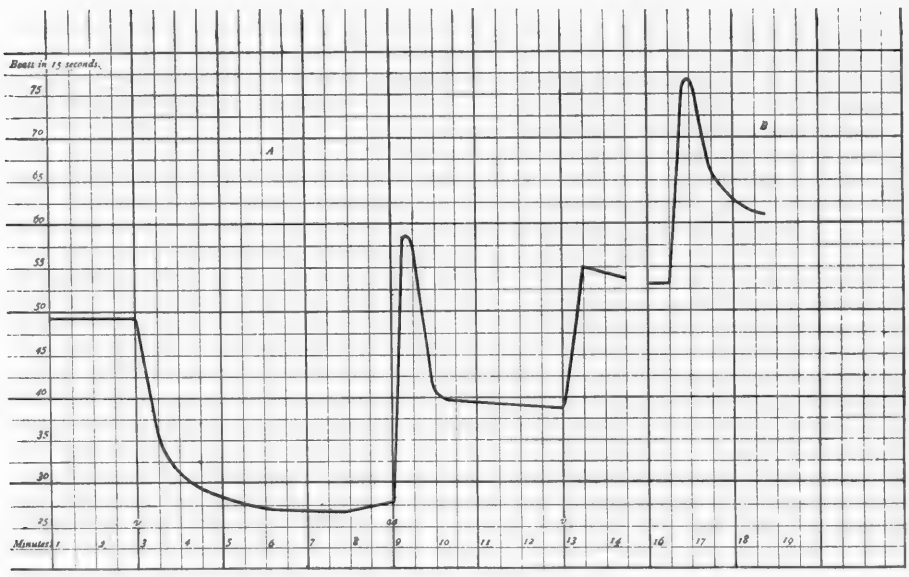


Fig. 1.—Stimulation of the accelerators during a prolonged stimulation of the vagus. The ordinates represent the heart rate in 15 seconds; the abscissæ the time in minutes.

***A.* The vagus was stimulated from *v* to *v* (10 minutes); the accelerators from *a* to *a* (15 seconds).**

***B.* Stimulation of the accelerators alone (15 seconds).**

Comment on these figures is scarcely necessary. They show that a stimulation of the vagus of sufficient strength to cause a decrease of the heart rate of 43.2 per cent is not only completely overcome by a stimulation of the accelerators, but that the latter causes an acceleration of 18.1 per cent above the rate at which the heart was beating

before the vagi were stimulated and an actual acceleration of 108.9 per cent. That the effect of the vagus on the other hand was not lost is shown by the fact that the maximum rate reached while both nerves were stimulated was but 58½ beats in 15 seconds as compared with 77 when the accelerators alone were stimulated; or while the acceleration above the normal rate was but 18.1 per cent in the former case, it was 45.3 per cent in the latter.

It might be thought that if the vagus and accelerators are purely antagonistic, a stimulation of the accelerators of sufficient strength to cause an acceleration of 45 per cent would just neutralize the effect of the vagus or cause but a very slight acceleration above the normal when the vagus was being stimulated with a current of sufficient strength to cause a slowing of 43 per cent, while in this experiment there was an acceleration of 18 per cent. However, it must be remembered that in general a slowly beating heart is more powerfully influenced by a stimulation of the accelerators than is one beating more rapidly; moreover, there are so many other factors entering into the problem that we could scarcely expect the result to be the exact algebraic sum of the results of the separate stimulations.

Results similar to the above have been obtained in experiments upon cats,* as the following table will show.

Cat. Ether. Vagi and accelerators cut. L. vagus stimulated; 4 interruptions per second of primary circuit; secondary coil 10 cm. R. annulus stimulated; secondary coil 11 cm.

hr.	min.	sec.	Heart-beats in 20 seconds.	Remarks.
2	53	20	42	
		40	23	Stimulation of vagus begun.
	54		20½	
	55		29	
	56		30	Heart slowed 28.5%.
		20	45½	Accelerators stimulated for 20 seconds.
		40	38	Acceleration of 51.6%
	57		34	
	58		30½	
4	2		30	
	23		30	Stimulus off vagus.
		20	38	

* Dr. D. W. Harrington and I have since obtained similar results in an experiment upon an opossum.

2.

Stimulation of the Vagus during a Prolonged Stimulation of the Accelerators.

The following experiments will serve to illustrate this side of the subject; a somewhat similar experiment will be described in the next section of this paper.

Young dog. Morphine and ether; curare. Vagi and accelerators cut. R. vagus stimulated; primary circuit interrupted $3\frac{5}{8}$ times per second; secondary coil at 4, later at 5 cm. L. annulus stimulated with ordinary induced current; secondary coil 15 cm. The vagus was first stimulated alone twice for the purpose of comparison.

hr.	min.	sec.	Heart-beats in 15 seconds.	Remarks.
12	35		48−	
			41½	Vagus stimulated 15 seconds; coil 5 cm.
	37		47	
			40−	Vagus stimulated 15 seconds; coil 4 cm.
	41		46	
		15	57	Stimulation of accelerators begun.
		30	56	
		45	55+	
	42		46−	Vagus stimulated 15 seconds; coil 4 cm.
		15	54+	
	43		54	
		15	48	Vagus stimulated 15 seconds; coil 5 cm.
		30	52½+	
	46		53½	
		15	46	Vagus stimulated 15 seconds; coil 4 cm.
		30	52+	
	47		53	
		15	47	Vagus stimulated 15 seconds; coil 5 cm.
	48		53+	

Some of these results are shown in Fig. 2.

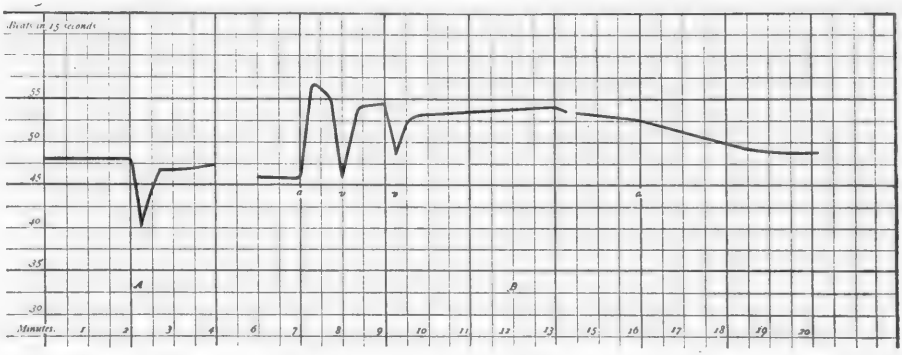


Fig. 2.—Stimulation of the vagus during a prolonged stimulation of the accelerators.

***A*. Stimulation of the vagus alone (15 seconds).**

***B*. The accelerators were stimulated from *a* to *a* (9 minutes); the vagus was stimulated twice (at *v* and *v'*) for 15 seconds.**

The first stimulation of the vagus in this experiment just overcame the effect of the stimulation of the accelerators and the heart was brought back to its normal rate; that the accelerator effect was not lost, however, is shown by comparing the rate of the heart when the vagus alone was stimulated (not quite 40 beats in 15 seconds) with that when both nerves were being stimulated (46 beats in 15 seconds). Stimulation of the vagus a second time, with a weaker current, caused a diminution of the accelerator effect, but the heart was not brought back to its normal rate. The two subsequent stimulations of the vagus show how constant were these results.

3.

Stimulation of the Vagus and Accelerators begun simultaneously.

The results of stimulating the two nerves simultaneously (a) for short periods (ten to fifteen seconds) and (b) for longer periods (several minutes) will be described in this section.

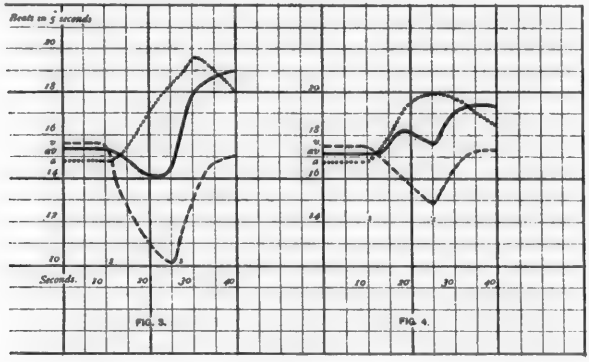
a. ***Simultaneous stimulation of the vagus and accelerators for short periods.***—Experiments will be described first in which the vagus was

stimulated with the slowly interrupted current, and the accelerators with the ordinary rapidly interrupted current. Each nerve was frequently stimulated alone to obtain figures for comparison. The results are arranged in the form of tables. In the first column is given the time; in the second, the nerve or nerves stimulated; in the third, the duration of the stimulation; in the fourth, the number of heart beats (d) during the stimulation, (b) in the interval corresponding to the duration of the stimulation immediately preceding, and (a) the number in the interval immediately following the stimulation; in the last column is given the change in the heart rate in per cent, the minus sign indicating a slowing and the plus sign an acceleration.

Dog. Morphine and ether; curare. Vagi and accelerators cut.

hr.	min.	sec.		seconds.	b.	d.	a.	
5	2	40	R. vagus; coil 0 cm.; 4⅜ interruptions per second.	15	47½	35	45	−26.4%
	5	30	R. annulus; coil 12 cm.	15	45−	51½	56½	+21.1%
	8	10	Both nerves; coils, etc., as above.	15	47	44	55	−6.3%

These results are shown more satisfactorily in Fig. 3, in which the heart beats are given in periods of 5 seconds.



Figs. 3 and 4.—Stimulation of the vagus and accelerators begun simultaneously. The ordinates represent the heart rate in 5 seconds; the abscissæ the time in intervals of 10 seconds; "*a*" stimulation of the accelerators alone; "*v*" stimulation of the vagus alone; "*a v*" stimulation of the two nerves simultaneously. The stimulations continued in each case for 15 seconds (from *s* to *s*) and followed each other at short intervals. The strength of the current was different in the two cases.

In this case the figures representing the result of stimulating the two nerves simultaneously are not far from being the algebraic sum of the figures obtained when the two were stimulated separately. These figures show conclusively that neither nerve has overcome the effect produced by the other; both have made their influence felt and to almost equal degrees, the inhibitory effect slightly predominating. After the stimulation the accelerator effect appeared to almost the same extent as when this nerve was stimulated alone, as was described by Baxt. This latter fact is readily understood when we remember that the accelerators have a long after-effect, while the vagus has not.

The results of a few subsequent stimulations made in the same experiment will be given to illustrate the effect of altering the strength of the stimuli. In the first table it will be observed that the number of vibrations per second of the oscillating rod was increased.

hr.	min.	sec.		seconds.	b.	d.	a.	
5	50		R. vagus; coil 0 cm.; 5⅔ vibrations per second.	15	49½	33½		−32.3%
	51		Vagus; coil, etc., as above. R. annulus; coil 12 cm.	15	49½	37	56	−25.2%

The current by which the annulus was stimulated was now strengthened by moving the secondary coil up to 10 and then to 8 cm.

hr.	min.	sec.		seconds.	b.	d.	a.	
5	52	30	Vagus (as before). R. annulus; coil 10 cm.	15	49	44½	56	−9.1%
	54	30	Vagus (as before). R. annulus; coil 8 cm.	15	51	44	56	−13.7%

The vagus effect still predominated, though to a less degree. It will be observed that the second increase of strength in the stimulus applied to the accelerators did not cause a corresponding increase in the effect upon the heart; such irregularities frequently occurred, but still the effect of the stimulation of the accelerators is plainly seen if the rate of the heart during the stimulation of the vagus alone (33½ beats in 15 seconds) is compared with that during the stimulation of the two nerves (44 in 15 seconds).

The current by which the vagus was stimulated was weakened by

diminishing the rate of the oscillating rod, and now the accelerators slightly predominated, as is shown in the following:

hr.	min.	sec.		seconds.	b.	d.	a.	
5	57		R. annulus; coil 8 cm. R. vagus; coil 0 cm.; 3½ interruptions.	15	52	54	57½	+3.8%
	59		R. vagus (as above).	15	52	47	48½	−10.0%
6	5		R. annulus; coil 8 cm.	15	51½	57	58	+10.6%

These results are shown in Fig. 4 (p. 168).

In the foregoing experiment there was a tendency for the inhibitory effect to predominate; in the following the tendency was rather for the accelerator effect to be more marked.

Small bitch. Morphine and ether; curare. Vagi and accelerators cut.

hr.	min.	sec.		seconds.	b.	d.	a.	
3	49		R. annulus; coil 14 cm.	15	34½	44	47	+27.5%
	52		L. vagus; coil 5 cm.; 3¾ interruptions per second.	15	33½	25		−25.3%
	59		Both nerves; coils, etc., as above.	15	32½	35½		+9.2%

The stimulus for the vagus was now made stronger and the nerves again stimulated.

hr.	min.	sec.		seconds.	b.	d.	a.	
4		3	R. annulus; coil 14 cm. L. vagus; coil 4 cm.; 3¾ interruptions per second.	15	34−	34½	46	+4.4%

The current by which the accelerators were stimulated was now weakened, but one of the above-mentioned irregularities occurred.

hr.	min.	sec.		seconds.	b.	d.	a.	
4	7		L. vagus; coil, etc., as above. R. annulus; coil 16 cm.	15	32½	37½	45½	+15.4%
4	10		Vagus (as above).	15	33−	25+		−24.2%
4	15		Vagus (as above). R. annulus; coil 17 cm.	15	31	30½+	43½+	−1.0%

These tables show that when the stimuli applied to the two nerves are properly selected, the effect of one nerve can be made exactly to

counterbalance that of the other. Similar figures could be given from many other experiments. Irregularities, such as were pointed out above, frequently occurred when the results of the use of stimuli of different strengths were compared with each other; but all the experiments, without a single exception, lead to the same conclusion, viz., that when the two nerves are stimulated simultaneously with stimuli at all comparable in strength (as judged by their separate effects upon the heart), the effect of each is plainly visible during the stimulation; the stimulation of one has never caused the complete obliteration of the effect of stimulating the other. If, however, the stimulation of one nerve is very strong in comparison with that of the other, then its effect alone may appear. This is sufficiently well known when the vagus is stimulated with a strong current; the following experiment shows that the reverse may occur, namely, the accelerator effect alone appear.

Dog. Morphine and ether. Accelerators cut. R. vagus intact. Central end of l. vagus stimulated with the ordinary induced current, and the heart thus slowed reflexly. The accelerators were stimulated with the slowly interrupted current.

hr.	min.	sec.		Duration of stimulation.	Heart-beats. b.	Heart-beats. d.	Change of heart rate in %.
3	44		Vagus; coil 10 cm.	20 sec.	52	47½	−8.6%
	47		R. annulus; coil 5 cm.; 3⅔ interruptions per second.	20	54	67½	+25.0%
	50		Both nerves; coils, etc., as above.	20	55	69½	+26.4%
	52	30	Vagus; coil 10 cm.	20	57	48½	−14.9%

Later in this experiment the peripheral end of the vagus was stimulated with the ordinary rapidly interrupted current and the accelerators with the slowly interrupted current; as the following figures show, the results are the same as when the methods of stimulation were reversed, as was the case in the experiments previously quoted. The slowly interrupted current was usually used to stimulate the vagus only because it seemed to give, as a rule, more constant results.

hr.	min.	sec.		Duration of stimulation.	Heart-beats. b.	d.	a.	Change of heart rate in %.
4	10		L. vagus; coil 21 cm.	15 sec.	39	34½	37½	−11.5%
	11	30	L. vagus; coil 21 cm. R. annulus; coil 5 cm.; 3⅜ interruptions per second.	15	38	41+	48	+7.9%
	13		L. vagus; coil 21 cm.	15	37	33	37	−10.8%
	15		Both nerves; coils, etc., as above.	15	36½	42	46½	+15.3%
	17		L. vagus; coil 21 cm.	15	37½	34+	37	−9.3%
	19		Annulus (as above).	15	36½	46½	49	+27.4%
	21		Both nerves; coils, etc., as above.	15	37−	44+	46½	+18.9%
	23		Vagus; coil 21 cm.	15	36	34½	35½	−6.9%

During these stimulations the irritability of the inhibitory nerves seemed to decrease, that of the accelerators to increase.

(b). *Simultaneous stimulation of the vagus and accelerators continuing for some time.*—Having found that when the two nerves are stimulated together for short periods, the effect of either can be neutralized by that of the other, so that the rate of the heart is scarcely affected, the effect of stimulating both for a longer period was tried.

As was pointed out at the beginning of this paper, however, this problem is somewhat different from the one we have been discussing, for now the possibility of the exhaustion of one or the other of the nerves must be considered. It is well known that the heart can be kept beating at a very slow rate for many hours by stimulating the vagus; I have been unable to find references to any experiments bearing upon the question of the fatigue of the accelerator nerves in mammals. Boehm,* it is true, says it is doubtful whether these nerves can be fatigued at all; but he does not seem to have stimulated them for periods longer than two minutes, and he is certainly not justified in drawing such a conclusion from stimulations of so short a duration.

I have performed a large number of experiments in order to determine how easily the accelerators are fatigued, or whether they are fatigued at all; the results of these experiments I hope soon to publish in full. Although these results are complicated and difficult to interpret, I think the following general conclusions may be drawn from them. When a moderately strong stimulus is applied to the accele-

* Boehm, *loc. cit.*

rators the rate of the heart rapidly rises to a maximum and remains at this level for a very variable period, occasionally for 8 or 10 minutes, but usually for a much briefer period. The rate then decreases, at first very rapidly and then very slowly; in many cases it reaches an almost constant level, which it may maintain as long as the stimulation continues. Frequently this constant level has almost coincided with the rate at which the heart was beating before section of the nerves, and this may be taken to represent the normal rate of the heart. The rate reached during a long-continued stimulation of the accelerators has seldom, if ever, in my experiments remained greater than the normal (using "normal" as above); usually it has been less, though still greater than that at which the heart was beating immediately before the stimulation began.

The fact that the heart can, by stimulating the accelerators, be maintained at its maximum rate for but a very short time might be attributed either to fatigue occurring in the cardiac muscle or in the endings of the nerves, or, as Professor Howell suggested, to a local effect upon the nerve at the point stimulated, that is, to what Professor Howell has called "stimulation fatigue."* In fact both of these factors seem to be involved; there is undoubtedly a local effect upon the nerve at the point stimulated which is the first cause of the decrease of the heart rate, but there also seems to be distinct evidence, which will be presented in a future paper, of fatigue occurring in the heart itself.

In any case the heart cannot be kept in a condition of maximum acceleration or beating at a rate much above what we may consider the normal rate for more than a very few minutes, offering in this respect a marked contrast to its conduct upon stimulation of the vagus.

What will be the final result of stimulating the two nerves together for a long period? Will the accelerators become completely exhausted and then the result be as if they were not being stimulated at all and the vagus exert its full influence? It is evident that the answers to these questions have interesting bearings upon the problem as to the manner in which the nerves affect the heart, and especially upon Gaskell's theory of the metabolic functions of these nerves. I hope

* Howell, Budgett and Leonard, *Journal of Physiology*, xvi, p. 311, 1894.

to investigate this question more fully in the near future, but will give here a few figures from experiments bearing upon it. In these experiments the local effect of the stimulus on the accelerators is disregarded, which I think may be done without affecting the general conclusions. In the first experiment recorded below the accelerators had been stimulated several times earlier in the experiment, so that they were probably more easily fatigued than they would otherwise have been.

Bitch. Morphine and ether; curare. Vagi and accelerators cut. R. vagus stimulated by slowly interrupted current; secondary coil 0 cm.; 7 interruptions per second of the primary circuit. R. annulus of Vieussens stimulated with the ordinary rapidly interrupted current; secondary coil at 15, then at 17 cm.

hr.	min.	sec.	Hearts-beats in 10 seconds.	Remarks.
3	19	30	46	
		40	37	Stimulation of vagus begun.
		50	34	
	20		33+	
	21		34½	
		40	34½	
		50		Stimulation of accelerators begun.
	22		51	
	23		49−	
	24		47+	
	26		45½−	
	28		45½−	
	30		45−	
	31		44+	
	33		43	
	34		42½	Stimulus off annulus.
	35		37½	
	36		36+	
	38		35−	
		10	43½	Stimulation of annulus begun; coil 17 cm
		20	47½	
		30	48	
	39		45	
	40		44	
	42		42½	
	43		41½	
		10		Stimulus off annulus.
		20	36½+	
	45		45+	

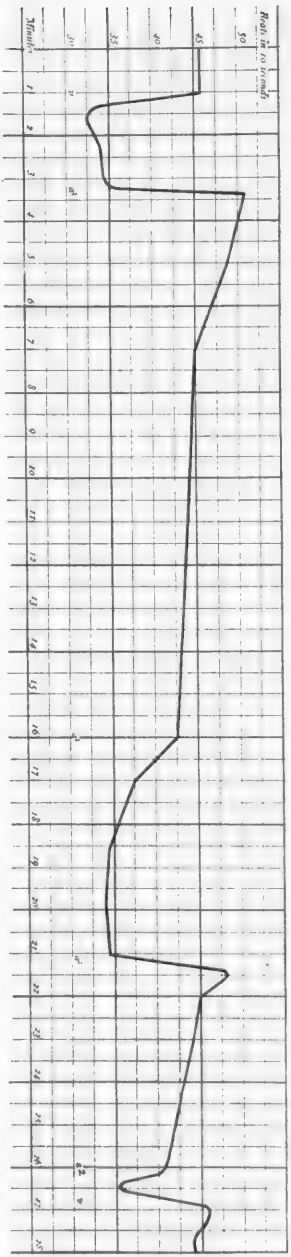


Fig. 5.—Long-continued stimulation of the vagus and accelerators. The ordinates represent the heart rate in 10 seconds; the abscissæ, the time in minutes. The vagus was stimulated from v to v (25 minutes); the accelerators were stimulated twice—from a^1 to a^1 (12½ minutes) and from a^2 to a^2 (9 minutes).

We see that in this experiment when the two nerves were stimulated together neither completely overcame the effect of the other in 12½ minutes, though the vagus gradually decreased the effect of the accelerators. That the effect of the stimulation of the accelerators was not completely overcome is shown by the fact that the heart rate is greater during the combined stimulation than during that of the vagus alone; also when the stimulation of the accelerators was discontinued, the heart rate quickly fell to what it had been under the influence of the vagus alone. It will be noticed that during the stimulation of the two nerves the heart rate fell below what it had been before the stimulation began; what the result would have been had the stimulation continued still longer it is impossible to say. (See Fig. 5.)

In the following experiment the nerves were stimulated together for more than half an hour. Changes in the condition of the animal almost necessarily occurred in such a long time; the depth of the anæsthesia and the temperature of the animal doubtless varied. The blood pressure fell and the heart was beating more slowly after than before the stimulation. The results, however, are interesting and very suggestive.

Bitch. Morphine and ether; curare. Vagi and accelerators cut. R. vagus stimulated; secondary coil 2 cm.; primary circuit interrupted 4 times per second. R. annulus stimulated; coil 15 cm. Several stimulations of the annulus had preceded the one described here.

hr.	min.	sec.	Heart-beats in 15 seconds.	Remarks.
12	20	45	61	
	21		68	Stimulation of accelerators begun.
		15	70	
		45	67	
	22		56	Stimulation of vagus begun.
		15	52½	
		30	46	
		45	56	
	24		57½	
	26		57½	
	28		57	
	30		57	
	32		56½	
	36		56	
	38		55−	
	40		54½−	
	42		53½	
	44		54	
	46		53½	
	50		53½+	
	52		54	
	53		54+	
	55		53½	Stimulus off vagus.
		30	60½	
	56	45	59	
	57	15	49½	Stimulus on vagus.
	58		50+	
	59		52+	
1			52½	Stimulus off accelerators.
	1	15	48	
	3		47	
	5		45	Stimulus off vagus.
		30	52½	

These figures show that after the two nerves had been stimulated together for about twenty minutes, the heart was beating at a rate which remained nearly constant (53½ to 54 beats in 15 seconds) for the next 13 minutes, *i. e.*, till the stimulation of the vagus ceased. That this rate is a result of the effects produced upon the heart by the stimulation of the two nerves is indicated by the fact that as soon

as the stimulus was removed from the vagus the heart rate increased from 53½ to 60½ beats in 15 seconds. Of course it may be objected that this was merely the return of the heart to its normal rate, which had been 61 before the nerves were stimulated, and the conclusion drawn that the accelerators had become completely exhausted and were no longer exerting any effect upon the heart. But the rate after the stimulation was but 51 in 15 seconds, and it is very probable that this number, rather than 61, represents the normal rate at this period of the stimulation. All doubt, however, as to whether the stimulation of the accelerators was still producing an effect upon the heart is at once removed by examining the figures immediately following. These show that when the vagus was again stimulated and the heart was beating at the rate of 52 beats in 15 seconds, taking the stimulus off the annulus caused the heart rate to fall to 45 in 15 seconds, which was the slowest rate reached during the experiment.

This experiment shows that the heart can be kept beating for a considerable period of time at a rate not far from the normal, but one which is determined by the stimulation of the vagus and accelerators. This is the result which I think would be expected on the theory that the vagi are anabolic and the accelerators katabolic nerves, provided that the two nerves were stimulated to about equal degrees. What the result would be of stimulating the nerves for a long period with currents unequal in strength my experiments are not sufficiently numerous to decide, but they suggest the following: When the vagus effect is the stronger, the heart rate finally reached is one below the normal, but above that produced by stimulation of the vagus alone; on the other hand I have failed so far to see a case in which stimulation of the accelerators kept the heart beating above the normal rate for a very long period, though, as in the experiment quoted above, it might maintain the rate at the normal, notwithstanding a continuous stimulation of the vagus.

Such results as the above, which my experiments so far indicate, might, I think, be easily explained on Gaskell's theory, for we know that stimulation of the vagus will keep the heart slowed almost indefinitely, and if this be due to an anabolic action of this nerve, the

weak stimulation of nerves causing katabolism, *i. e.*, the accelerators, would be expected to destroy a part, but only a part, of the products of this anabolism, and the final effect would be that the heart rate would reach a level below the normal, but still above that caused by the stimulation of the vagus alone; and this seems to be what actually occurs. On the other hand it is difficult to see how katabolic nerves, however powerfully stimulated, could cause any prolonged increase of the heart rate above the normal, for the supply of the products of anabolism would soon be exhausted, even though the anabolic nerves were being stimulated at the same time; in other words, the katabolism cannot be greater than the anabolism for any great length of time. Hence the final result of a long-continued stimulation of the accelerators with a maximum stimulus combined with a weaker stimulation of the vagus would be the production of a heart rate about the normal, but which is still determined by the two stimulations. This is what seems to have actually occurred in the second experiment described above; that the stimulus applied to the accelerators was at least a maximal, and probably a super-maximal, stimulus is shown by the fact that a weaker current caused the same maximum acceleration.

I desire to add, however, that these views are put forward only tentatively; subsequent experiments may show them to be incorrect. The chief object in introducing these experiments here at all is to show for what long periods the two nerves may be stimulated together without either overcoming the effect produced by the other.

CONCLUSION.

The experiments described in Part IV of this paper show that in whatever manner the problem of the relation of the vagus to the accelerators is approached, whether the accelerators are stimulated during a stimulation of the vagus, or the vagus during a stimulation of the accelerators, or both are stimulated simultaneously, either for a short or for a longer period, the result is the same, viz., the effect upon the rate of the heart is determined entirely by the relative strength of the stimuli applied to the two nerves. If the stimuli are of approximately the same strength, as judged by the effect of stimulating the nerves separately, the rate of the heart is but slightly

affected; if the stimulus applied to the vagus is the stronger, the heart is slowed; if it is weaker, the heart is accelerated. In all cases the result of stimulating the two nerves simultaneously is approximately the algebraic sum of the results of stimulating them separately; sometimes the inhibitory effect slightly predominates, but not more frequently than does the accelerator effect. Moreover, the two nerves may be stimulated simultaneously for a considerable period of time without either completely overcoming the effect of the other.

Thus as far as their effect upon the rate of the ventricular beat is concerned, the vagus and accelerator nerves seem to be purely antagonistic; the statement that a minimal stimulation of the one can completely overcome a maximal stimulation of the other is undoubtedly incorrect, and the hypotheses as to the mode of action of these nerves upon the heart, based upon this statement, lose their chief support.

NOTE.

Results very similar to those described in the above paper were obtained by Mr. Conant and myself in an experiment upon a crab.* One of the accelerator nerves of this animal was stimulated a number of times during the standstill produced by a long-continued stimulation of one of the inhibitory nerves; in each case the heart began to beat and continued beating during the stimulation of the accelerator, stopping completely again as soon as this stimulation was discontinued. The accelerator alone was now stimulated and a marked acceleration obtained; while this stimulation continued the inhibitory nerve was stimulated, with the result that while the acceleration was diminished the heart rate was still about the normal. The stimulus was removed from the accelerator nerve, while that on the inhibitory remained; total inhibition resulted.

It is interesting to note that in the crab the irritability of the inhibitory and accelerator nerves seems to be much more nearly equal than is the case in the mammal; in the above experiment a stimulus of sufficient strength just to cause total inhibition was sufficient to cause an almost maximal acceleration.

* For a description of the cardiac nerves in the crab, see the article by Conant and Clark, *The Journal of Experimental Medicine*, i, p. 341, 1896.

ON THE ACTIVE PRINCIPLE OF RHUS TOXICODENDRON AND RHUS VENENATA.

By FRANZ PFAFF, M. D., Ph. D.
(*From the Pharmacological Laboratory of the Harvard Medical School.*)

Plate X.

Of all the cutaneous eruptions caused accidentally by vegetable matters, that produced by the different kinds of Rhus is probably the most common in this country. The common occurrence of poisoning with poison ivy and poison sumach, and the lack of any rational treatment for this, led me to try to isolate the active principle of these plants, in the hope that a knowledge of its characteristic properties might serve as the basis for such treatment.

It is, as is well known, the general belief of the public and of most physicians that the eczematous conditions which occur in many persons after handling such plants may be caused also by emanations from the plant, the active principle being thought to be a volatile substance. The two previous attempts which have been made to isolate the poisonous principle failed. Nevertheless the investigators making them shared the general opinion that the active substance is volatile.

The first who attempted to isolate the active principle of Rhus toxicodendron was J. Khittel.* He attributed the action of poison ivy to a volatile alkaloid.

Later, in 1865, John M. Maisch published† a preliminary notice "On the Active Principle of Rhus toxicodendron." He could not agree with Khittel's statements and denied the presence of a volatile alkaloid. He thought that he had found a new volatile acid, which he held to be the active principle and which he called toxicodendric acid.

As Maisch's article is the only paper which is now quoted when one

* Wittstein's *Vierteljahresschrift für praktische Pharmacie*, vii, 348–359, 1858.
† *Proceedings of the American Pharmaceutical Association*, 1865, 166.

speaks of the active principle of Rhus, I may be allowed a few remarks upon it. After having failed to obtain the volatile alkaloid of which J. Khittel spoke, Maisch performed the following experiment. He enclosed in a tin box a lot of freshly collected leaves of poison ivy, and introduced into this box a number of moistened test papers. The next morning he found that the blue litmus paper had been colored strongly red, whereas curcuma and red litmus paper were unaffected. He writes regarding this experiment: "This single experiment was at once a conclusive proof that the exhalations of these leaves contained a volatile acid, and that the poisonous properties were most likely due to it." Maisch describes further how he obtained an impure watery solution of his toxicodendric acid by maceration of the leaves, expression and distillation of the expressed liquid. In preparing his acid, Maisch suffered from a copious eruption and the formation of numerous vesicles on the back of his hands, fingers, wrists and bare arms. He says further: "Several persons coming into the room while I was engaged with it were more or less poisoned by the vapors diffused in the room, and I even transferred the poisonous effects to some other persons merely by shaking hands with them. The dilute acid, as obtained by me, and stronger solutions of its salts, were applied to several persons, and eruptions were produced in several instances, probably by the former, though not always, which was most likely owing to the dilute state of the acid."

Maisch did not isolate his acid nor any one of its salts; he never had the substance in question chemically pure. He concludes his article with the following words: "Even in the chemical history of this acid, nearly everything is to be found out yet by further researches. If my time permits I may attempt to prepare it in larger quantities and in a more concentrated form, and to determine its composition." No further publication by Maisch or by any other investigator has appeared.

Maisch's view has been generally held to be correct and his toxicodendric acid has been accepted as the active principle. We find his article quoted by Husemann.* Lewin† mentions toxicodendric acid

* Aug. Husemann, A. Hilger und Theod. Husemann, Die Pflanzenstoffe, 2te Aufl., 867.

† L. Lewin, Die Nebenwirkungen der Arzneimittel, 766.

as the probable active principle. In the U. S. Dispensatory and by Dr. James C. White,* the toxicodendric acid of Maisch is recognized as the active principle of Rhus, and speculations are made as to what should be the treatment of the dermatitis caused by this acid. But Husemann† remarks that Buchheim held the active principle of Rhus to be cardol, and Schmiedeberg‡ and Boehm§ quote Buchheim's supposition without mentioning the toxicodendric acid at all.

As has been stated, Maisch never isolated his toxicodendric acid in a chemically pure state. He proved only the presence of a volatile acid. He further noticed the characteristic eruption on his own skin while he was working with the poison ivy. Persons coming to the laboratory at this time were often poisoned there. He observed also that an eruption sometimes followed the application of the impure solution of this acid to the skin. From these very rudimentary experiments he draws the wholly unwarranted conclusion that his acid must be the active principle.

To demonstrate the pharmacological actions of any one substance, the first thing necessary is to have this particular substance chemically pure. Experiments made with impure substances have only a very restricted value, if any, and can never be conclusive as to the real nature of a substance and its properties. Whether Maisch's toxicodendric acid, or any other substance, is the active principle of Rhus can be decided only by preparing these substances chemically pure and studying their action.

Before describing the methods of isolation and purification of the different substances obtained from poison ivy and poison sumach, I wish to state in a few words the classification of the different cutaneous irritants as given by Schmiedeberg.‖ According to this author, all skin irritants may be divided into three different groups. In the first or "turpentine group" are comprised all substances which at ordinary temperature are not too difficultly volatile. To this group belong the

* James C. White, Dermatitis venenata. Boston, 1887.
† Loc. cit.
‡ O. Schmiedeberg, Grundriss der Arzneimittellehre, 3te Aufl., 1895, 222.
§ R. Boehm, Lehrbuch der Arzneiverordnungslehre, 2te Aufl., 1891, 374.
‖ Op. cit., 213–224.

different turpentines, many ethereal oils of the vegetable kingdom, many substances of the fatty series of organic compounds, and also aromatic compounds like benzol, etc. The more volatile a substance, the quicker its action; formic and acetic acids, for example, act more quickly than the less volatile acids of the same series.

If substances which are volatile have in addition a very stimulating action upon the skin, as is seen in a very high degree in the case of mustard oil, their action will be a very vigorous one. They produce in a very short time all degrees of general stimulation: pain, redness of the skin, exudative inflammation with formation of bullæ, formation of pus and necrosis of the tissue. The second group of skin irritants is represented according to Schmiedeberg specially by mustard oil.

In the third group of skin irritants are classed by the same author all substances which have a specific irritant action upon the skin, but which are not volatile at ordinary temperature. Their action will be slower than the substances of the preceding groups, and as a rule less vigorous.

This is the only scientific classification of cutaneous irritants that has been made, as far as I know, and all substances known to us as such irritants can easily be brought into one of the three groups according to their action.

Without knowing the real active principle of Rhus, the clinical history of the dermatitis caused by the unknown substance leads one necessarily to suppose that the poisonous substance should belong to Schmiedeberg's third group of skin irritants, that is to say, it ought to be a non-volatile specific skin irritant. Of course only experiments with the isolated and pure substance can settle this question definitely.

I will now briefly describe my own experiments. My first endeavor was to get Maisch's acid pure and to determine its composition.

An aqueous solution of Maisch's acid was easily obtained by distilling the finely divided fresh plant in a current of steam. By previously acidulating with dilute H_2SO_4 the yield of Maisch's acid was considerably increased. The addition of H_2SO_4 did not alter the nature of the acid, as was proved by separate distillation of the drug without

the use of H_2SO_4. The distillate, which showed strongly acid reaction, after neutralization with an alkali left on evaporation the corresponding salt. In this way the barium and sodium salts were prepared. After repeated crystallization from dilute alcohol the salts were secured chemically pure, as was shown by the analyses of the products of different preparations.

The acid distillate, which, as already noticed by Maisch, had a peculiar odor, contained besides the acid, traces of an oil, which could be separated from the solution by shaking it with ether. The ethereal solution left on spontaneous evaporation a very small amount of an oily substance with quite an agreeable odor. To this oil we shall refer later.

The crystallization of the impure barium salt of Maisch's toxicodendric acid was accomplished by dissolving the salt in water, heating the solution nearly to the boiling point and adding alcohol until a faint cloudiness appeared. The glass was now covered and set aside. On cooling, long crystals appeared, which sometimes were over 1 cm. long. The sodium salt was obtained in beautiful white crystals, often 2 and 3 cm. long. The latter salt was deliquescent. Both salts were very easily soluble in water.

The analyses of the salts of different preparations gave the following results:

ANALYSES OF THE BARIUM SALT.

I. Barium salt, air-dry, 0.9750 gramme lost on heating 0.0620 gramme H_2O, and gave on ignition with H_2SO_4, 0.8378 gramme $BaSO_4$.

II. 0.5440 gramme barium salt (of the same preparation) lost by 110° C. 0.0353 gramme H_2O, and gave 0.4670 gramme $BaSO_4$.

III. 0.5800 gramme (of the same preparation as used in analyses I and II) lost 0.0380 gramme H_2O at 110° C. The dried substance gave 0.2773 gramme CO_2 and 0.4215 gramme $BaCO_3$. The water was lost in this analysis.

IV. 0.5340 gramme of the same substance lost at 110° C. 0.0350 gramme H_2O, and gave 0.1198 gramme H_2O, 0.2535 gramme CO_2, and 0.3879 gramme $BaCO_3$.

V. 0.4586 gramme substance of another preparation, dried at 105–110° C., gave 0.1178 gramme H_2O, 0.2303 gramme CO_2, and 0.3573 gramme $BaCO_3$.

VI. 0.3465 gramme of a third preparation gave 0.0221 gramme H_2O and 0.2969 gramme $BaSO_4$.

ANALYSES OF THE SODIUM SALT.

I. 0.4715 gramme air-dry substance lost on heating to 105–110° C. 0.1875 gramme H_2O, and gave on ignition with H_2SO_4, 0.2450 gramme Na_2SO_4.

II. 0.6430 gramme lost on heating to 105–110° C. 0.2558 gramme H_2O, and gave on ignition with H_2SO_4, 0.3370 gramme Na_2SO_4.

III. 0.7092 gramme lost 0.2830 gramme H_2O by 105° C., and gave on ignition with H_2SO_4, 0.3677 gramme Na_2SO_4.

BARIUM SALT.

Water Found					Calculated for
I.	II.	III.	IV.	VI.	$Ba(C_2H_3O_2)_2 + H_2O$.
6.36	6.49	6.56	6.55	6.39	6.59 per cent H_2O

	Found						Calculated for
	I.	II.	III.	IV.	V.	VI.	$Ba(C_2H_3O_2)_2$.
Ba,	53.95	53.96	54.08	54.07	54.18	53.84	53.71
C,			18.69	18.58	18.45		18.83
H,			*	2.66	2.85		2.35

SODIUM SALT.

Water Found			Calculated for
I.	II.	III.	$NaC_2H_3O_2 + 3H_2O$.
39.76	39.78	39.90	39.71 per cent H_2O

Sodium Found			Calculated for
I.	II.	III.	$NaC_2H_3O_2$.
27.95	28.17	27.94	28.05 per cent Na

On heating one of the salts with sulphuric acid and alcohol the characteristic odor of acetic ether was developed. The watery solution of the alkaline salt gave, on addition of ferric chloride, a blood-red color. In short, Maisch's toxicodendric acid proved to be nothing but acetic acid, and was therefore not the real cause of the peculiar dermatitis caused by poison ivy.

The real active principle of the Rhus plants was obtained in an impure state by extracting the plant with alcohol, distilling off the alcohol, washing the black, oily residue with water and taking it up in ether. The ethereal solution was then first washed with water and with dilute solution of sodium carbonate and again with water. By evaporating the ether an oily substance of very dark color was obtained, and this when applied to the human skin showed the well-known lesions occurring after contact with some part of the Rhus plant.

This oil was far from being a pure substance, as could be easily seen by simply treating it with alcohol. One part of it dissolved

* The determination of H_2O in this analysis was lost.

easily in this vehicle, leaving a residue which was soluble with difficulty even in warm alcohol. The isolation and purification of the active principle from this oily mixture offered some difficulties. The process finally adopted was the following: The oily mixture was treated with 10 to 15 times its bulk of 95 per cent alcohol at ordinary temperature. The alcoholic solution, decanted from an insoluble resinous residue, deposited on standing more of the resinous matter taken up by it. After standing two days the alcoholic solution was filtered and an alcoholic solution of lead acetate was added to it. The precipitate formed was of a very dark color, and was not the pure lead compound of the oily active principle, for the obtaining of which fractional precipitation had to be resorted to. The later precipitates so obtained consisted of the lead compound of the oil in a pure state. The first precipitates were contaminated with the resinous material referred to above. From the filtrate of these lead precipitates another oil was obtained by getting rid of the excess of lead with ammonium sulphide, diluting with water and shaking with ether. On allowing the ether to evaporate spontaneously, an oil with an agreeable odor was obtained. This oil seemed to be identical with that obtained in small quantity in the distillation of the finely divided plant in a current of steam. This oil apparently had no irritant action upon the skin.

The free active oil was separated from its uncontaminated lead compound, obtained as just described, by decomposition with ammonium sulphide and gave the characteristic skin eruptions. The purity of the lead compound of the oil was demonstrated by quantitative analyses of two different preparations, one from the fruit of Rhus toxicodendron and the other from the leaves; the plants having been collected at different seasons and in different localities.

I. 0.2563 gramme lead compound (dried at 105° C.) gave 0.1406 gramme $PbSO_4$.

II. 0.2192 gramme of the same preparation gave 0.1106 gramme H_2O and 0.3610 gramme CO_2.

III. 0.3001 gramme (of another preparation) gave 0.1640 gramme $PbSO_4$.

IV. 0.2400 gramme gave 0.1152 gramme H_2O and 0.3949 gramme CO_2.

	Found				Calculated for $C_{21}H_{30}O_4Pb$.
	I.	II.	III.	IV.	
Pb,	37.49		37.32		37.43
H,		5.61		5.33	5.42
C,		44.94		44.88	45.56

The free oil obtained from the pure lead compound has as yet not been analysed.*

For this poisonous oil, which is not cardol, from which it differs in chemical properties, I propose the name of Toxicodendrol. It was found in all parts of the plant—in the stems, branches, roots, leaves and fruit—its amount, however, varying, the fruit and leaves containing most. The oil was found in Rhus toxicodendron as well as in Rhus venenata. We were not able to find any essential difference between the oil obtained from the two different species. Rhus venenata seemed to contain more oil than Rhus toxicodendron.

A few quantitative estimations were made of the crude oil, that is to say, the mixture of the active oil contaminated with the resinous matter and the oil not giving a lead precipitate. It was found that the leaves of Rhus toxicodendron contained 3.3 per cent crude oil, whereas the fruit contained 3.6 per cent, and the stems and branches of the same plant only 1.6 per cent. The oil obtained from the fruit seemed to be the purest; the one from the leaves, and especially from the branches, containing more resinous matter.

Toxicodendrol is easily soluble in alcohol, ether, benzol, chloroform, etc., but is insoluble in water. Toxicodendrol is decomposed easily by heat, but only slowly at ordinary temperature. A sample of it, which had been left for thirteen months in an open porcelain dish, was partly converted into a resin, but the remaining oil proved to be just as active as before.

The active oil was prepared also from plants which had been collected during the winter, after being covered with snow for weeks. Old stems and branches of the plant which had been kept in the laboratory over a year and were perfectly dry gave still quite a considerable amount of active oil. The only difference between the fresh and the

* The results as published here were obtained by me more than a year ago. Through other work, my time has been taken up so that I could not proceed further. This research is now being continued in the laboratory. We shall first prepare other derivatives of the oil to establish a definite molecular formula, and further, we shall compare more accurately the two oils obtained from Rhus venenata and Rhus toxicodendron, to see whether they are really identical or not.

old plant was that the former was less contaminated with resinous matter.

The action of the oil isolated from Rhus toxicodendron seemed to be identical as to kind and intensity of action with that from Rhus venenata. Clinical observation had established long before that the dermatitis caused by either plant is identical in appearance. Poison sumach was thought to be only a stronger poison. Should both poisons even in final tests prove to be identical, the difference in the strength of the action of poison ivy and of poison sumach would be easily explained by the fact that the latter contains more of the active oil.

As an example of the effect of the isolated oil upon the human skin, I shall describe a case of poisoning with the oil from Rhus venenata. I relate this case not because the oil used was from Rhus venenata, but because the person upon whom the experiment was performed, Dr. Cleon Melville Hibbard, was in former years often accidentally poisoned in a severe manner when handling poison oak or poison sumach. Furthermore, Dr. Hibbard was extremely interested in this question and was self-sacrificing enough not only to be the subject of the experiment, but also to take minute notes of the progress of the experiment and to have the affected parts photographed twice.

The following extract is taken from his notes:

"1894, October 13, 5 P. M. On the anterior surface of the left forearm, three inches from the wrist, some of the oil extracted from Rhus venenata was placed with a glass rod. The forearm was then wrapped with absorbent cotton and bandaged.

11 P. M. Left forearm had a very slight burning sensation. An area the size of a cent about the point of application of the oil was reddened. New dressing put on.

Oct. 14, 7 A. M. Burning sensation slightly increased. The area which was inflamed last night has now about 10 vesicles dotted over it, and the redness has increased to the size of a dollar.—P. M. The area of inflammation now about 1½ inches in diameter. The vesicles seen in the morning have become confluent and appear as one large blister the size of a ten cent piece.

Oct. 15, 7 A. M. The left forearm itched considerably during the night. Redness now 2 inches in diameter and becoming somewhat

swollen.—P. M. The arm is now considerably swollen and slightly painful.

Oct. 16, 7 A. M. Arm more painful and tender. The photograph taken this A. M. (Plate X, Fig. 1) gives a good idea of the distribution of the vesicles and the degree of swelling. Applied a paste of zinc oxide ℥ss, amyli, vaseline āā ℥ss at 12 M. and again at 7 P. M.

7 P. M. The vesicles are larger and redder than this A. M. There are a few (6 or 7) vesicles on index finger and a few scattered all around the forearm.

9 P. M. Swelling extends now from knuckles to the elbow. Pronation and supination painful, feels very uncomfortable. Paste used with light bandage, instead of the heavy bandage of absorbent cotton as heretofore.

Oct. 18, A. M. Blisters began to break down yesterday and considerable watery fluid ran from the arm. Dressed the arm several times with the above-named paste. Last night applied a mixture of 2 per cent carbolic vaseline and boracic acid ointment. The swelling extends now from between the fingers to above the elbow. The area first affected does not look so red now, nor is it so tender as yesterday. On the edge new vesicles are coming out. The whole arm throbs and burns considerably.

11 P. M. Removed the point of infection, an area 1 inch by $\frac{3}{4}$ inch which had become black and necrotic; it was about $\frac{1}{8}$ inch in depth. Arm dressed with carbolic vaseline.

Oct. 19, 10 A. M. Arm is considerably swollen to 5 inches above elbow, and some small vesicles here are quite visible. The extent of the swelling can be seen from the second photograph (Plate X, Fig. 2), which is blurred somewhat with the zinc paste. Yet it can be seen that even the finger-joints were noticeably swollen. The whole arm has been oozing since the 17th, and required dressing several times a day. The vesicles are now becoming confluent and form blisters the size of a dollar all over the arm.

Two days ago two small blisters appeared on the index finger of the right hand; they have been washed most thoroughly with soap and water and the scrubbing brush, and have not spread much in the last 24 hours. During the daytime have carried the arm in a sling since the 16th of October. At night supported arm on a pillow outside of the sheets and blankets, with only an ointment bandage covering it.

Oct. 20, at Dr. Pfaff's suggestion, I stopped applying any ointment and began to scrub the whole arm with soap and water. Although it burned some when rubbed, it was not very painful, and the relief obtained from such treatment was as soothing as after applying the carbolic vaseline.

The arm was treated thus several times a day. Went in town to-day, and as it was painful to bend the elbow, I did not carry the arm in a sling; as a result of this and the car ride, the œdema of the arm became very great, and this caused considerable pain. Supporting it upon a table while sitting in a low chair for several hours gave much comfort and caused an œdematous swelling to collect in the axilla, which disappeared the next day. The vesicular eruption is now at a standstill.

Oct. 23. From Oct. 21st the swelling gradually disappeared, and to-day arm is back to normal size. The blebs continued to fill with serum in places until to-day, the parts first affected drying up 3 or 4 days ago. An interesting point is that from the time that water and the scrubbing brush were used, and the ointment stopped, the spreading also stopped, and it left patches on the back of the hand unaffected.

At the height of the inflammation in the arm an intense pruritus ani started up, but 2 or 3 days treatment with soap and water caused it to disappear.

Oct. 27. After Oct. 23 desquamation began, and by to-day this process is complete. Now new tissue covers the whole surface that was covered with blisters. The time taken for the healing of the arm from the beginning of the inoculation was just two weeks. There were never any general symptoms, excepting one day a slight fever."

Dr. Hibbard's case ran the ordinary course of a severe dermatitis caused by poison ivy or poison sumach, and as we find so well described by Dr. J. C. White.* The photographs accompanying this article show the appearances presented 65 hours and 6 days after the application of the oil (see Plate X). All the usual features of an accidental poisoning were reproduced in this case of intentional poisoning. Even the treatment applied for the first 8 days was such as is employed by expert dermatologists who have had a large experience of this peculiar dermatitis.

Besides Dr. Hibbard's case, I have produced two similar severe cases of dermatitis by means of the oil extracted from Rhus toxicodendron. In these two cases no medicine whatever was used. The eruption in these cases was just as severe, as was also the œdema, as in Dr. Hibbard's case. In these two cases spreading of the affection to other parts of the body was entirely prevented, simply by keeping the

* Loc. cit.

inoculated arm bandaged constantly. Changes of the bandage were not made by the inoculated person, but by other hands, so that a transfer of the poisonous oil from the inoculated forearm to other parts of the body of the same person was impossible.

To test the strength of the toxicodendrol and the latent period of the dermatitis, I made dozens of experiments upon myself and others, who kindly gave not only their assistance for these experiments, but also underwent the discomfort and pain which they entailed.

In all cases, without a single exception, the free purified toxicodendrol, obtained by decomposition of its lead compound, proved to be a very severe skin irritant. The minutest traces of it were active. The degree of activity varied, however, in different persons. In some 0.1 milligramme produced many hundreds of vesicles and considerable œdema of the forearm; in one person even $\frac{1}{200}$ mg. caused such a severe dermatitis that the whole forearm was extensively swollen and the pain so severe that sleep was impossible for a few nights. Even $\frac{1}{1000}$ mg. dissolved in two drops of olive oil proved to be active in one person. Severe itching, a few dozen of vesicles and localized œdema followed the application of that small dose.

The latent period varied, as in accidental poisoning, in wide limits. In some persons redness, swelling, itching, and even papules, were noticed from 18 to 24 hours after the application of the oil. In other cases 7 and even 9 days elapsed before the first symptoms were noticed. In most cases the first symptoms appeared four to five days after the application of the oil.*

The skin eruption may be produced also on rabbits, if the fur is cut short. In these animals the latent period seems to be longer, as the skin eruption makes its appearance, as a rule, in from one to even two weeks. Swelling, localized redness and the formation of papules, vesicles and crusts are well marked. The eruption, conforming to

* I may give here an interesting case of accidental poisoning showing the latent period of poison ivy. On a Tuesday three men were helping me to divide about 10 k. of freshly collected poison ivy. All these showed the following Sunday the first symptoms of poisoning. Neither before nor after this Tuesday had these persons been near poison ivy. In their case, therefore, the latent period was five days.

the non-volatility of the poison, remains perfectly localized, and only the tissue near the point of application undergoes pathological changes. The continued action of the toxicodendrol on the rabbit's skin is followed by an increase in length of the hairs of the spots affected, the fur, too, becoming more shiny. In the case of one dark rabbit the new hairs were of a lighter color.

Another well-known cutaneous irritant, cantharides, is used with some benefit in practical medicine as a hair restorer, where the pathological condition is due to a malnutrition of the skin. But it is not probable that toxicodendrol can act as a substitute for cantharides, as the great œdema caused by minute amounts of the oil will doubtless prevent its use for this purpose.

The effects on the system following an internal administration of toxicodendrol have been studied in a few rabbits. The oil was given to these animals either in alcoholic solution or dissolved in pure olive oil. These solutions were given *per os* through a stomach tube. The irritant properties of toxicodendrol were most marked on the kidneys, producing nephritis and conspicuous fatty degeneration of this organ. In one case the stomach of the animal was found to be the seat of extreme diphtheritis. The symptoms after internal administration of toxicodendrol to rabbits were complete loss of appetite, suppression of urine, and later albuminous urine (0.5 per mille albumin in one case), with blood corpuscles and renal epithelium. Some animals died shortly after administration of the oil. The autopsies revealed no cause of death in these cases, only slight redness of the mucous membrane of the stomach being observed.

The cases recorded in medical literature in which death has followed after severe poisoning with poison ivy may have been caused by renal complications. It is not impossible that these persons may have suffered previously from some chronic renal trouble, and after being poisoned with poison ivy or poison sumach, enough of the poisonous oil was absorbed from the skin to cause an acute exacerbation of the already existing disease of the kidney, and thus to lead to a fatal end.

This explanation is suggested merely as an hypothesis to explain the few fatal cases following poisoning with Rhus. Whether in fact

the recorded cases of fatal issue after poisoning with poison ivy had any real connection with these poisonous plants is open to doubt, as the history of these cases is open to criticism, and it is especially to be remarked that in not one case has an autopsy been made. The real cause of death may have been, therefore, entirely overlooked.

As to the rational treatment of Rhus poisoning, it is to be noted that the poisonous oil, as we have already repeatedly stated, is non-volatile. It is very sticky and will cling persistently to parts which may have become contaminated with it. It oxidizes in contact with air and is transformed into a solid resin. But this process is a very slow one. This resinification of the oil may be hastened by heat and alkalies, even by a solution of carbonate of sodium, but still the process remains a very slow one. The metallic compounds of the oil, after decomposition, leave again the oil with all its irritant properties. The poisonous oil is soluble in most of the common solvents and fatty substances, but is insoluble in water.

From all the chemical properties just enumerated, the rational indication in a case of Rhus dermatitis would be to get rid of the poisonous oil that may still be on the skin of the affected person as quickly as possible, no matter in what stage the eruption may be.

This can be done by vigorously washing the affected and exposed parts with soap, water and a scrubbing brush, that is to say, mechanically. As the active principle is very soluble in alcohol and gives with lead acetate a precipitate which is nearly insoluble in alcohol (the copper and iron compounds are also easily obtained as precipitates), other processes may be employed to remove the oil. The exposed parts may be washed repeatedly with fresh quantities of alcohol and a scrubbing brush. The poisonous oil would be thus removed in alcoholic solution; or still another way of operating would be to wash the exposed parts with an alcoholic solution of lead acetate. In this case the poisonous principle would be first transformed into its insoluble lead compound and then washed away with alcohol. The washing must be done thoroughly when alcohol is employed, as otherwise the alcohol would only help the spreading. The nails have to be cut short and also perfectly cleaned with the scrubbing brush. Oily

preparations, or anything which dissolves the poisonous oil, if used and not *immediately* removed, would only spread the poison, giving it a larger area on which to work. This spreading was well seen in Dr. Hibbard's case. The vaseline ointment used in the treatment dissolved the oil which adhered to the point of application, and thus caused the spreading of the eruption. That the proposed treatment does not cure the already inflamed parts is self-evident.

How can the commonly accepted idea be explained that poisoning may occur without actual contact with the poisonous plants when the active principle is a non-volatile substance?* The activity of toxicodendrol in minutest traces may make it possible for a few pollen grains of poison ivy to cause skin eruption; and the few cases of action at a distance, which are so often quoted, may conceivably be thus explained. But, in my opinion, it is more than doubtful if ever a case of ivy poisoning has occurred without direct contact with the plant or some article which has been in contact with the plant. The long latent period of the eruption in some cases may obviously render mistakes extremely easy as to the occasion when contact with the plant really occurred.

I wish to express my thanks to Dr. Hibbard and to the other gentlemen who kindly took an active part in the experiments made upon the action of toxicodendrol on the human skin.

DESCRIPTION OF PLATE X.

Photographs of arm, showing dermatitis produced by an oil extracted from Rhus venenata.

Fig. 1.—65 hours after application of the oil.

Fig. 2.—6 days after application of the oil.

* I have used more than 25 k. of fresh poison ivy and a few k. of poison sumach. Hundreds of persons passed through the laboratory during the time that these plants were handled, extracted, distilled, etc. In not one single instance was a person poisoned who did not come into actual contact with the plant or the free oil.

FIG. 1.

FIG. 2.

THE HISTOLOGICAL CHANGES PRODUCED BY RICIN AND ABRIN INTOXICATIONS.

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PLATES XI–XIV.

I.

The study of the effects of the living pathogenic organisms upon the animal body has been succeeded by an era in which especial attention has been directed to the influence of their soluble products. The researches of Oertel* upon human diphtheria, of Babes† and of Welch and Flexner‡ upon the experimental form of the disease, the latter including the effects of the soluble products of the growth of the bacillus diphtheriæ, and of Flexner§ upon the pathological changes caused by the soluble products of the streptococcus erysipelatos alone and combined with the diphtheria toxin, as well as studies of the toxic substances contained within the dead bodies of the cholera spirillum, have shown that these toxins may be very potent agents of metamorphosis of cell and tissue, and make it more than probable that in most instances, if not in all, they are the chief instruments of bacterial attack.

Bodies similar to the toxalbumins of bacterial origin have been obtained from the higher plants and even from certain normal animal fluids. Thus from the seeds of the castor plant, Ricinus communis, the jequirity bean, Abrus precatorius, ricin and abrin have been

* Oertel, Die Pathogenese der epidemischen Diphtherie. Leipzig, 1887.

† Babes, Untersuchungen über den Diphtheriebacillus und die experimentelle Diphtherie. Virchow's *Archiv*, cxix, 460, 1890.

‡ Welch and Flexner, The Histological Changes in Experimental Diphtheria. *The Johns Hopkins Hospital Bulletin*, ii, 107, 1891.—The Histological Lesions produced by the Toxalbumin of Diphtheria, iii, 17, 1892.

§ Flexner, The Pathology of Toxalbumin Intoxication. *Johns Hopkins Hospital Reports*, vi, 1896.

respectively isolated by Stillmark,* Sidney Martin,† and Hellin;‡ and from the blood serum of several species of eels the principle, ichthyotoxicum, has been obtained by A. Mosso§ and Springfeld,¶ while Kobert|| has found the toxicity of the bites of the true spiders to be due in part to the toxalbumins introduced into the wounds. The toxalbumins in the bodies of the last-named animals bear no definite relation to their poison glands, for in some species the whole body, including the extremities and eggs, are, according to Kobert, bathed in a fluid containing toxalbuminous substances.

All of the substances now designated " toxalbumins " do not belong to the albumins in the strict sense of the term. Some are globulins, others nucleo-albumins, peptones or albumoses, and still others belong to none of these groups. They are the albumin-digesting, starch-converting, glucoside-splitting enzymes of animal or vegetable origin.** Thus the poisons secreted by the poison glands of various kinds of serpents are now classed with the toxalbumins, although they are far from being simple compounds. Weir Mitchell and Reichert†† believed that they had obtained from rattlesnake venom two principles, a globulin and a peptone; but the latter is not a true peptone as physiological chemists now understand the term; it indeed seems more nearly allied to the albumoses.‡‡ The poison yielded by Abrus is likewise composed, according to Sidney Martin,§§ of a globulin and albumose, of which the former is several times more toxic than the latter.

*Stillmark, Ueber Ricin. *Arbeiten des Pharmacologischen Institutes zu Dorpat*, iii, 1889.

† Sidney Martin, The Toxic Action of the Albumose from the Seeds of Abrus precatorius. *Proc. of the Royal Society*, xlvi, 100, 1889.

‡ Hellin, Der giftige Eiweisskörper Abrin und seine Wirkung auf das Blut. Inaug. Diss. Dorpat, 1891.

§ A. Mosso, Die giftige Wirkung des Serum der Mureniden. *Arch. f. exp. Path. u. Pharmakol.*, xxv, 111, 1889.

¶ Springfeld, Ueber die giftige Wirkung des Blutserums des gemeinen Fluss-Aales (Anguilla vulgaris). Inaug.-Diss., Greifswald, 1889.

|| Kobert, Lehrbuch der Intoxicationen. Stuttgart, 1893, 329.

** Kobert, ibid., 706; Hammersten, Lehrbuch der physiologischen Chemie, 3te Aufl. 37, 1895.

†† Mitchell and Reichert, Researches upon the Venoms of Poisonous Serpents. Smithsonian Contributions, Washington, 1886.

‡‡ Sidney Martin, op. cit., 106.

§§ Ibid.

My previous researches on the histological changes caused by the bacterial toxalbumins led me to extend my studies to include those which are induced by the phytalbumoses, ricin and abrin, and later, the alterations in the tissues of the rabbit brought about by the injection of the blood serum of the dog. The last group of experiments were carried out in conjunction with Dr. Ethel Blackwell, and will be reported at another time.

The samples of ricin and abrin used in these experiments were procured in the open market and came from Merck's laboratory. They fulfilled the usual conditions regarding solubility, coagulating temperature, etc., and were highly toxic. For purposes of my experiments they were dissolved in a 10 per cent solution of sterilized salt solution, and when the total quantity was not used immediately, the residue left for a subsequent experiment was preserved by the addition of 0.5 per cent of carbolic acid. Before injection the solutions were diluted with sterile distilled water, so as to render them of an equal density with physiological salt solution.* The animals which served for this study were rabbits, guinea-pigs and mice. They were chosen with some care, many having been raised in the laboratory, and none were subjected to inoculation which did not at the time appear to be healthy. The material to be injected was introduced subcutaneously, intraperitoneally or intravenously. In mice the first method was employed exclusively; in guinea-pigs, the first or the second; and in rabbits, all three severally. The quantity of poison injected varied within narrow limits, as it was my aim in every instance to introduce into the animals an amount which would always prove a certainly fatal dose.

In giving the results of my studies the individual protocols will not be detailed, and only the extremes of dosage and duration of life need be stated. It does not seem possible to make a distinction in respect to the pathology of the process depending upon amount of toxic agent and duration of life where the latter is short and does not exceed a

* A preliminary communication concerning this study appeared in the *Medical News*, August 4, 1894, under the title, "The Pathologic Changes caused by certain so-called Toxalbumins."

week or ten days. On the other hand the more chronic forms of intoxication are likely to be associated with pathological changes which differ very much in degree, if not in kind, from those of the acute cases.

The autopsies upon the dead animals were performed as soon as possible after death, the attempt having been made so to choose the time of inoculation as to bring about death during the day hours. While in the majority of cases this procedure was successful, in some it failed. It was always my aim to obtain the tissues in the fresh state, as the finer histological methods are much less efficient when applied to tissues in a state of even incipient post-mortem decomposition. The changes in the intestinal mucosa in particular are not to be relied upon unless these conditions are fulfilled. In order to obtain trustworthy results the intestine should be hardened without disturbing its mucous surface and with its contents adhering to it.

As hardening agents, alcohol, graded or 95 per cent from the first, bichloride of mercury, formalin, Flemming's and Hermann's solutions were employed. The sections were made in paraffin or celloidin, more often the latter, and stained with hæmatoxylin and eosin, carmine, magenta, safranin, and, for special purposes, Weigert's fibrin stain. In order to ascertain the presence of fat in situations from which it is normally absent, or of estimating its amount where it is commonly present, fresh frozen sections were employed. These served, at the same time, for the study of other forms of degeneration.

The close relationship existing between the bodies ricin and abrin and certain bacterial toxins has already been alluded to. The studies of Kobert made it appear probable that these bodies, although obtained from two entirely different sources, yet possess identical properties. The experiments of Ehrlich* on the production of immunity in mice and guinea-pigs from these substances proved that, although they possess many features in common, yet they are essentially distinct.

The observations of Kobert and his pupils were limited to the action

* Ehrlich, Experimentelle Untersuchungen über Immunität. I. Ueber Ricin. II. Ueber Abrin. *Deutsche med. Wochensch.*, 1891, 976 and 1218.

of these bodies on the blood, and incidentally on such organs as the gastro-intestinal tract, the lesions of which he attributed to the vascular thromboses believed to exist there. Stillmark failed entirely to discover lesions in the parenchymatous organs. Ehrlich also considers the pathological changes in the viscera (stomach and intestine) to be the results of vascular disturbances.

My experiments have led me to entirely different conclusions regarding the mode of action of these substances and to consider them as acting upon cells and tissues much like the bacterial toxins. Indeed, while this resemblance is more or less striking, the pathogenic behavior of ricin and that of abrin are, under these circumstances, so nearly alike that except for Ehrlich's important observations I should feel inclined with Kobert to regard them as physiologically identical.

The doses employed varied, in the rabbit, from 0.1 to 3 milligrammes per kilo of body weight, and in the guinea-pig from 0.25 to 1 milligramme per kilo of body weight. The duration of life following inoculation was subject to fluctuation. The shortest period observed was in the rabbit (3 milligrammes ricin per kilo) which succumbed as early as in six hours, and the longest in the guinea-pig (1.5 cc. of a 1 to 200,000 solution) which survived about 6 weeks. A few animals after a varying period of illness recovered entirely and were protected from the effects of subsequent inoculations.

The picture presented by animals which have been subjected to inoculation with either substance differs somewhat and depends upon the dose, and still more upon the mode of introduction of the poison. In all cases there is a rise of temperature, averaging about two degrees; diarrhœa is present, the stools being of a bloody character unless the animal succumbs very quickly; the urine is always albuminous and contains tube casts and in rare cases red blood corpuscles; severe convulsions, opisthotonos and great general weakness, preceded by a fall in temperature, are likely to occur before the end.

The gross pathological changes after intravenous inoculation consist, first, of punctiform hæmorrhages, most abundant in the peritoneal cavity, where they are scattered over the omentum and beneath the serous covering of the intestine, mesentery and abdominal parietes.

Similar ecchymoses, smaller in number, are found beneath the serous covering of the solid abdominal organs and of the heart and lungs. The peritoneal cavity contains, in a large majority of instances, a great excess of fluid, which is often opaque and hæmorrhagic. As much as 100 to 150 cc. of such fluid may be present. On the intestine, in which the fluid presents a bloody aspect, the subserous hæmorrhages are very numerous. Several pregnant female animals were used for experimental purposes, and in all free hæmorrhages had taken place into the fœtal membranes. No gross lesions of the blood-vessels were discovered anywhere in the abdomen; the fluid and accompanying blood corpuscles evidently passed out of the injured vessels by transudation and diapedesis. On the other hand no excess of fluid existed in either the pleural cavities or the pericardium.

The lymphatic glands generally showed enlargement, they were softened and congested or hæmorrhagic; the mesenteric glands more especially were swollen. One of the most striking features was the condition of the intestinal mucosa. In the case of very rapid death (6 hours) the intestine was filled with opaque, almost fluid contents much resembling cholera stools. The mucous membrane, as a rule, was pale; Peyer's patches were much swollen, elevated and of a white color. In the other case the appearances are usually somewhat different; while the intestine is always distended, the contents are semi-fluid, tinged with blood, and the general surface of the mucosa is greatly congested and beset with pin-point hæmorrhages. Peyer's patches become very prominent and deeply congested, the intervening mucosa showing less swelling. The whole picture suggests the *surface reticulée* of the typhoid intestine. Actual ulceration, contrary to the views expressed by other writers (Kobert, Ehrlich), was never found. The fact that these observers apparently did not take the precaution of confirming their opinions by microscopical examinations necessarily throws doubt upon the existence of such lesions. The mucous membrane of the stomach was congested in all cases. In a few instances superficial losses of substance in the mucosa were noted. Around these signs of reaction were missed. It should be noted that in one rabbit (No. 8) there existed in the stomach a congested patch the size

of a quarter of a dollar, over which the epithelium was entirely necrotic.

The spleen was uniformly swollen, of dark color and of less firm consistence than normal. The swelling was apparently of the splenic pulp. The liver was always dark in color and hyperæmic. Focal lesions, resembling the areas of necrosis described first by Welch and Flexner* in experimental diphtheria and now known to occur in many kinds of infection as well as in several intoxications, were always present. These were in some cases just beneath the capsule, in others within the deeper substance of the liver. They were most evident to the naked eye when in the former situation and, as often happened, when they were surrounded by a zone of hyperæmia or hæmorrhage. The other organs, save more or less hyperæmia, appeared to the naked eye normal.

Subcutaneous inoculation produced, besides the lesions mentioned, also local effects. In very acute cases the subcutaneous tissues presented an œdematous condition, which was often hæmorrhagic in character. The local lymphatic glands were now much enlarged and reddened. In more protracted cases a subcutaneous node formed, followed by necrosis, and eventually by sloughing of the skin.

II.

Lymphatic Glands.—The histological study may begin with a consideration of changes in the lymphatic glands. The extent of injury to a particular group of glands depends largely upon the mode of access of the poison, for when this is injected directly into the blood all the glands may be presumed to receive an approximately equal share; when, however, the poison is introduced beneath the skin, the nearest glands must receive a much larger quantity. The differences, however, in the extent of the affection of different groups of glands cannot depend upon this factor alone, for even in the instances of vascular distribution, not all the lymphatic glands suffer equally.

The channels of elimination of the poison from the body determine still another avenue of glandular affection in excess of the vascular

* Loc. cit.

form. It has been shown by Stepanoff,* and by Calmette and Delarde,† that ricin and abrin are removed from the body largely through the intestinal tract, and this elimination is accomplished, as I shall show, not without great injury to its constituent histological elements. It would also appear that a second absorption (resorption) from the intestinal tract may take place, in which case the mesenteric glands are more than ordinarily swollen, reddened and softened.

The histological changes in the lymphatic structures are in part productive, but chiefly degenerative in character, and affect the lymphoid cells, the most pronounced feature being death by fragmentation of cytoplasm and karyoplasm. In some lymphatic glands every node is affected, in others the lesions are relatively insignificant. The peri-follicular lymph sinuses and the lymphatic spaces beneath the capsule contain fragmented cells and large phagocytes (macrophages) loaded with metachromatic-staining globular particles. Within these channels, and more frequently in the peripheral parts of the follicles, karyokinetic figures are seen in small numbers. The medullary portion of the gland also suffers in a similar way. The most intense alterations are found in the inguinal and axillary glands in cases of subcutaneous inoculation. In extreme cases nothing remains of the original normal tissue of these glands. The swelling of cells and coincident hæmorrhages obliterate the peri-follicular lymph sinuses; the medulla is permeated with blood; the lymph cells in the follicles are converted into lightly staining nuclear fragments and feebly staining remnants of cell protoplasm (Plate XI, Fig. 1). A fine network of fibrin traverses these areas. The medulla shows no intact cells, but only fragments and altered protoplasm remain. Macrophages are abundant in the follicles and in the similarly affected lymph cords, and appear here, there and everywhere in the medullary part of the gland. Nuclear residues of all forms and sizes and particles of blood pigment are included in these bodies. The blood-vessels are often overcrowded with red corpuscles; coagula of any sort were entirely missed.

* Stepanoff, Études sur la ricine et l'anti-ricine. *Annales de l'Institut Pasteur*, x, 663, 1896.

† Calmette and Delarde, Sur les toxines non microbiennes, etc. *Annales de l'Institut Pasteur*, x, 675, 1896.

Intestine.—Of all the constituents of the intestinal mucosa, the one to feel the most severe effects of the poison is the epithelium. Here again the most marked alteration is the cell disorganization effected through transformation both of nucleus and cell body, although the picture is dominated by the changes in the former. All sorts of intensely staining bizarre forms appear within the protoplasm of the cells, from the minutest particle of chromatin to crescents, imperfect vesicles, agglomerations of particles with rosette and stellate forms and flask-shaped bodies. The protoplasm itself is granular and opaque, partly disintegrated or fused with neighboring cells. Many of the particles of nuclear material, exhibiting the most striking metachromatic coloring by the aniline dyes, have found their way into the lumina of the glands on one side and that of the intestine on the other (Plate XIV, Fig. 10).

The villi in the small intestine also suffer. The cells distributed within their delicate reticulum become increased in number, swollen and finally fragmented. The changes in the vessels themselves, consisting of necrosis of lining cells and circulating leucocytes, form a striking feature. The epithelium covering the villi, but especially that within the crypts, shows mitoses, which, in the latter situation, in cases of less severe injury may be numerous.

Congestion is a marked feature in the gastric and intestinal pathological processes, and hæmorrhage is not uncommon. The blood-vessels in submucosa and mucosa are over-distended, but no relative increase in white corpuscles is discernible. The vessels are not thrombosed; no trace of fibrin can be found in ordinary preparations or such as were stained especially for this material.

Ulceration in the true sense of the term does not exist. On the other hand there has been a free desquamation of necrotic epithelial elements which, together with fragmented cells and what resemble emigrated mononuclear or lymphoid elements, are piled up on the surface of the mucosa, mingling with the other intestinal contents. The whole may form a layer of some thickness, and may resemble superficially an exudate; it shows nothing of the nature of a genuine inflammatory product, and is as devoid of polymorphonuclear cells as of fibrin. It does, however, contain great numbers of bacteria.

The lymphoid tissue of the intestine suffers considerably. The lymphoid cells, which are scattered diffusely, go through the same evolutionary and involutionary changes as those in the collections forming the solitary follicles and Peyer's patches. The patches themselves show an increase in size, due partly to the swelling of the cells, œdema, congestion or hæmorrhage, and partly to the presence of large phagocytic cells and included cell fragments, or sometimes possibly to actual multiplication of the lymphoid elements.

The stomach is affected to a distinctly less degree than the intestine. Congestion is marked; hæmorrhages are relatively infrequent and of small size; necrosis of scattered cells exists to a limited extent; the surface epithelium may desquamate, leaving small foci open to the invasion of various kinds of bacteria already present, which may force their way for a limited distance into the gastric glands.

Spleen.—With some few exceptions it has been found that the bacterial toxalbumins affect the Malpighian bodies far more profoundly than the splenic pulp. It would appear as if in the case of the phytalbumoses the seat of most intense action is reversed. The follicles are, however, not without easily discernible lesions. Necrosis (preceded by swelling) of cells by fragmentation exists, affecting small and large cells, separated by only slightly affected or almost normal lymphoid cells; many of the degenerative products are included by phagocytes (Plate XIV, Fig. 8). These lesions are hardly comparable to those which are met with in the same specimens in the pulp. In these small animals there is every appearance suggestive of the blood within the pulp circulating in free and wide spaces lined with a high endothelium. The walls of the sinuses are very thin and attenuated and contain so few cells that the lesions are found especially in the blood-vessels and only to a slight extent outside of these. The degenerated cells in the splenic pulp are of every kind met with in this situation. As the whole number has received augmentation owing to the disease process, the total injury is much greater than could otherwise be accounted for. Endothelium, leucocytes, mononuclear and polymorphonuclear, red blood corpuscles and lymphoid elements all succumb to the destructive effects of the poison (Plate

XIII, Fig. 7). Globules and fragments of protoplasm and of nuclear substances, and small and large balls of golden yellow pigment, are sometimes found free, but chiefly within cells, many of which exceed in size those observed even in the most pronounced bacterial infections and intoxications. These giant phagocytes—veritable macrophages—are enormously swollen and loaded with an indiscriminate and incongruous mixture of parts of cells, entire altered cells and pigment, to which the metachromatic properties of many of the particles, when stained in safranin or magenta, lend a brilliantly variegated appearance. The ultimate destination of the macrophages is not clear; they are found in various stages of development within the sinuses; soon they occupy the width of a sinus, and in cross sections of apparently sound vessels they are to be found completely filling the lumina (Plate XIV, Fig. 9). The capillaries of the stroma may show only more or less cell degeneration or, what is of more interest, extensive fibrinous thrombi, which in some instances are present. The blood-vessels, except the capillaries, are widely open and contain red corpuscles of normal appearance.

Liver.—The pathological alterations are of two kinds; one only, however, will be considered in some detail. The mere swelling, increased granulation and fatty metamorphosis, which are found in the hepatic cells generally, need not be discussed, as these lesions are found in a great variety of conditions associated with altered nutrition and are well known. One of the common appearances in the liver is brought about by a great dilatation of the intralobular capillaries, which often causes a marked compression of the rows of liver cells. The packing of red corpuscles is very evident, and the individual outlines of these corpuscles may not be distinguishable, thereby suggesting the formation of thrombi of red corpuscles in the sense of Kobert and of Ehrlich. White corpuscles do not appear to be increased in number in the blood in general.

The more specific changes are not distributed equally throughout the entire liver, but are focalized. They affect, also, scattered individual cells and scattered groups of cells. These alterations are attended by necrosis, actual death of the cells, rather than by simple

nutritive disturbances, as in the diffuse lesions. The initial focal lesion is a swelling of the cells whereby the intervening capillaries may be compressed. Simultaneously the cell protoplasm becomes pale, homogeneous and transparent. The nuclei may still stain, but often only feebly. There is no evidence of pathological fatty metamorphosis at this stage, although the two processes may be associated. Very soon a further transformation of the affected cells occurs, the protoplasm now showing an increase in refraction, thus exhibiting the peculiar appearance to which the name "hyaline" has been applied. An especial characteristic of these altered cells is their capacity to fix acid dyes (such as eosin), which they take up with great avidity and retain with equal persistence. The hyaline change thus described may be limited to a small part of the cell, or it may affect entire cells or groups of cells occupying the whole field of the microscope (Plate XII, Fig. 3).

The behavior of the nuclei varies in different instances, often in the same section of the liver and not infrequently in the same necrotic focus. Perhaps the commonest feature is the loss of staining capacity, such as occurs in karyolysis from various other causes; but nuclear fragmentation or karyorhexis, which is a more striking change, is not wanting. An earlier change than the latter, and probably than either of the foregoing, is the diffusion of the chromatin and the resulting contraction and deeper staining of the nucleus (pyknosis). The appearances clearly indicate that the degenerative process begins at the centre and spreads towards the periphery, and in its course obliterates all the structures of the normal cell (Plate XII, Figs. 3 and 4). After the disruption of the nuclei their fragments may still be retained within the cell body and be further distinguished by marked metachromatic staining (Plate XIII, Fig. 5).

The hyaline transformation does not end the pathological process. Positively chemotactic substances are generated in the areas of cell necrosis, and thereby polymorphonuclear leucocytes are attracted to the areas of dead cells, and not a few of these leucocytes likewise undergo degeneration, often fragmenting and adding their quota to swell the general wreckage. These emigrated cells are found every-

where in the affected parts, in the capillaries, the stroma of the portal spaces, and between and invading the dead cells themselves. They undoubtedly aid in the disintegration of the necrotic masses and the removal of debris. A fibrinoid metamorphosis may affect a part or the whole of the area of dead cells. The outlines of the altered cells, which in all cases are accentuated, now become still more pronounced, and the cell substance about the same time begins to lose its homogeneous and refractive character and to assume a granular and even fatty or vacuolated appearance. Very soon all, or almost all, of the contents, save the much thickened walls (membranes ?) of the cell, disappear. The capillaries having previously been obliterated by the swelling, adjacent rows of cells are brought together, and as the cell contents vanishes, only the coalesced margins of cells are left, thereby producing an appearance like a network of fibrin (Plate XI, Fig. 2).

Hæmorrhages are common in the liver substance, themselves causing more or less damage to the tissue; small extravasations of blood may also take place into the disintegrating necrotic foci. From either cause hepatic cells, quite normal, or hyaline and necrotic, may be washed into the hepatic veins (Plate XIII, Fig. 6).

The blood-vessels of the liver suffer in a more marked degree than those of other organs, except of the local lymphatic glands and the spleen. The changes resemble those found in these organs, the most pronounced alterations being in the spots in which the dead liver cells are contained. Small, light, fibrinous thrombi, almost devoid of cells, may occur in capillaries in regions in which the liver cells are entirely healthy. They are, however, likely to be larger and more common in the areas occupied by dead cells. If attention be directed to the lymphatic spaces in the interlobular connective tissue, one is often surprised at the large amount of nuclear detritus which many of these contain. There can be no reasonable doubt that such an amount of nuclear material could not come from the cells lining the lymphatics, nor from those of the lymph. The only probable interpretation of this appearance is that this material represents largely unclear fragments and debris from the focal areas of necrosis of the liver parenchyma swept along by the lymphatic current.

Kidneys, Adrenal Glands and Heart.—The kidneys showed, in fresh frozen sections, fatty degeneration in some cases only of the tubular epithelium, in others of this and of the glomeruli as well. In very rare cases the glomeruli suffered more than the tubules. The main lesions are to be found in the hardened sections (Flemming's solution, etc.). They occur chiefly in the tubular epithelium, which shows besides the fatty change, hyaline (colloid) transformation and even necrosis, and in the blood-vessels, of which the glomerular capillaries especially are to be mentioned. The endothelium of the glomerular capillaries as a rule did not appear much affected; but within some capillaries leucocytes accumulated, and these rarely underwent fragmentation, or, assuming various bizarre forms, became hyaline, deeply staining, at times fused together, thereby forming imperfect thrombi. The cells of the capillary wall took no part in the process, and it was the rarest occurrence for some material, possibly fibrin, to be deposited upon the capillary walls so as to render them thicker and of a hyaline appearance. The glomerular, but chiefly the capsular epithelium, suffered severely, being degenerated and sometimes converted into ring-shaped bodies (*Schollen* of German writers).

The heart muscle in fully two-thirds of the fatal cases is the seat of fatty degeneration, which may affect almost all or only groups of the fibres. A severer lesion is swelling of the fatty muscle fibres and fragmentation of their nuclei, in other words actual necrosis of the muscle cells.

Hæmorrhages in the adrenal glands, especially marked in the medulla, are invariably present. The cells of the parenchyma and of the vascular endothelial tunic suffer degeneration. The lesions met with here are necrotic, being associated with karyorhexis and affecting, in the former, single cells or small groups. Attention is called to the resemblance of these lesions to those observed in experimental diphtheria.

The thyroid gland also shows much congestion and at times small extravasations of blood.

Brain.—A study of the alterations in the central nervous system

induced by ricin was kindly undertaken, at my suggestion, by Dr. Henry J. Berkley, whose results, with the chrome-silver method, have already been published.* In view of the fact that the silver stain gives only an incomplete picture of the finer lesions of the neurones, it has seemed desirable to supplement this method by others, the best at present being that of Nissl or some of its modifications. This work, which has already been begun, is not sufficiently advanced to warrant a discussion of the results in this paper. Berkley found in animals poisoned with this drug changes especially in the finest nerve processes and involving often wide areas. The alterations consisted of irregular swellings of the dendrites, accompanied by loss of the lateral buds or gemmulæ, followed by complete destruction of the dendrites to the cell body, which itself becomes swollen and more rounded in outline. The cells of the neuroglia, besides swelling and thickening of their extensions, showed no alteration.

Chronic Ricin and Abrin Intoxication.—That individual animals behave in an exceptional manner and succumb after a much longer period of time (6 weeks or longer) has already been pointed out. The pathological picture in such cases is widely different from that described, the extreme emaciation of the animals and the pigmentation of their viscera lending to it the features of a profound cachexia. The microscopical examination bears out this view. Of the acute lesions scarcely an indication can be found. The liver is uniformly dark, and if focal necrosis exists it is in process of organization (one case). Much blood pigment is found in the capillary walls and in cells within their lumina. The spleen shows the most profound changes, which concern not so much its specific elements, but which are to be regarded rather as a result of great hæmolysis. The splenic pulp is crowded with granules and globules of golden yellow pigment which is almost, if not entirely, enclosed in cells either in its sinuses or in its framework and vascular walls. The follicles only are almost devoid of this pigment. Treated with potassium ferrocyanide and hydrochloric

* Berkley, Report in Neurology, iii. *The Johns Hopkins Hospital Reports*, vi, 1896.

acid, all the pigmentary substance strikes a blue color, indicating the presence of an iron constituent more loosely combined than in the hæmoglobin whence it is doubtless derived (hæmosiderin ?). The pigment contained within the liver gives the same reaction. The kidneys may show circumscribed points of granular and fatty degeneration of the epithelium of the labyrinthine tubules, and in addition (one case) a focal increase of cellular connective tissue in the cortex, beneath the capsule, which had given rise to indentations on the surface of the organ.

A comparison of the histological lesions described in the foregoing pages with those found in many forms of bacterial infection and toxæmia demonstrates their essential similarity. The chief lesions, and the ones which are regarded as especially significant and characteristic, are those which are degenerative and focal in character, especially the focal necroses. Inasmuch as similar necroses in the liver and elsewhere play an important rôle, and one which is as yet not generally appreciated, in various human infections and intoxications, the observations recorded in this article are a contribution to our knowledge of the causation and histology of these lesions. As appears from the description, the toxic substances exert their effects upon individual cells, but not all the cells of the body show the same susceptibility to their action. While, as we have seen, lymphoid cells and epithelium are both affected, yet the former are implicated to a greater extent. Neither do all of the epithelial cells of the various organs suffer in equal degree; thus, for example, the cells of the liver are more affected than those of the adrenals and kidneys, and the cells of these latter organs more than those of the pancreas. Finally, in highly differentiated cells, at least, not all parts of the protoplasm need be equally affected by the poison. Not a few examples of partial degeneration of cytoplasm have been described in this article, and if Berkley's results obtained from researches upon the cerebral cortex are confirmed, the constitution of the protoplasm of the dendrites will be proved to be more susceptible than that of the cell bodies.

There is evidence already at hand which goes to prove that the

extent of cell injury in any particular organ is in a measure proportional to the functional activities exerted in dealing with the particular poison. The severity of the intestinal lesions in these forms of intoxication is most probably intimately associated with their eliminative functions.

It is far less easy to account for the focal character of the lesions in the organs, assuming the action to be due to a soluble substance contained within the circulating blood and fluids of the body. While these lesions are produced by the action of soluble toxic substances, their presence cannot be explained by supposing different degrees either of functional activity or of susceptibility to injury in the cells affected. Given an organ such as the liver or the spleen, to which the injurious agents are brought by the circulating blood, we are not justified in assuming either such an irregular function or varying resistance as a consideration of the affected cell groups would, according to this view, render necessary.

I desire to direct attention to another explanation, and one which is more in accordance with observed phenomena, accidental or experimental, than are the foregoing suggestions. I refer to the part played by the circulation of the blood in the affected organs, which I am fain to believe bears an intimate relation to such focally distributed lesions as are now under consideration. We have seen that the action of the poisonous agents is exerted in part upon the capillary walls. The necrosis, fragmentation and regeneration of endothelium indicate this. I would also point out that the injury to the capillary wall is nowhere so great as in the areas in which the necrosis is found. This fact suggests the possibility that in certain capillaries, in which the circulation was much diminished or was temporarily at a standstill at the time when the irritant acted with the greatest intensity, so much damage was done to the vessel wall that a freer transudation than occurred elsewhere took place into the tissues in the neighborhood, resulting in the destruction of cell groups. It is well known that the circulation is not equal in all parts of an organ at all times; this is especially true of the capillary circulation, which is subject to wide variations. Moreover, Cohnheim has shown that the lymph

flowing through a part will be more concentrated the greater the permeability of the vessel wall.

The existence of intracapillary thrombi composed of fibrin and leucocytes in the region of the necrotic cells in the liver was proven by Barker* in his studies upon malaria and by Schmorl† in his work on puerperal eclampsia, and allusion has been made to the occurrence of similar formations in some of my specimens. Both Barker and Schmorl consider it not improbable that these thrombi may have been the precursors of the cell death, an assumption not without pathological foundation. The distribution of the areas of degeneration in lymph gland, spleen, liver, etc., and the frequent involvement of the smallest islands of cells do not, however, agree with the usual findings in anæmic necrosis. Of further significance is the irregular distribution of the thrombi, which occur at one time where no necrosis exists, and at another are absent from considerable areas of cell-death. We have, again, the histological evidence of injury to the vessel walls, which is never absent where parenchymatous necrosis exists, and present even where this other finding is wanting. And if we recall the known relation between degeneration of the vascular endothelium and thrombus formation, it will scarcely be necessary to seek further for an explanation of the observed facts regarding thrombosis.

The uncertainty which must be felt in the study of uninjected specimens as to whether the apparently free capillaries and larger vessels are really open, is removed by examination of the injected organs, a procedure which was carried out in a number of instances of ricin intoxication.

In view of the findings in this study, the recent conclusion of Werhovsky,‡ that in abrin intoxication the essential lesion is swelling of groups of heart muscle fibres, is indeed surprising. He missed entirely the most characteristic and wide-spread lesions.

* Barker, A Study of Some Fatal Cases of Malaria. *The Johns Hopkins Hospital Reports*, v, 1895.

† Schmorl, Pathologisch-anatomische Untersuchungen über Puerperal-Eklampsie. Leipzig, 1893.

‡ Werhovsky, Beiträge zur pathologischen Anatomie der Abrinvergiftung. Ziegler's *Beiträge*, xviii, 115, 1895.

The fate of these lesions in those animals which do not succumb within the period studied, or which entirely recover, is known for at least the liver changes. The invasion of the foci of dead cells by leucocytes and the removal of the necrotic elements may, perhaps, be followed in some instances by regeneration and restoration of the integrity of the organ. I think that it oftener happens that in the place of the dead cells a new tissue develops, which leads not to restoration of the original elements, but to the formation of a scar. The evidence for this rests upon the rich proliferation of tissue cells in capillaries and pre-existent connective tissue about these foci and the gradual invasion of these foci by such cells. While in the series of experimental cases described in the foregoing pages only the acute forms of intoxication have been fully considered, in the study of rabbits poisoned by the blood serum of the dog, in which rabbits similar focal necroses occur, evidence has been found that the areas of necrosis may be replaced by new growths of connective tissue and that thereby a form of cirrhosis may result.

I take pleasure in acknowledging my indebtedness to Dr. William H. Welch for his valuable advice while carrying on these studies in his laboratory.

DESCRIPTION OF PLATES XI–XIV.

PLATE XI.

Fig. 1.—Focal area of necrosis in lymphatic gland (follicle), showing altered cells, fragments of nuclei and metachromatic nuclear particles. Phagocytosis of detritus. Magenta staining. Homogeneous immersion objective $\frac{1}{12}$ in.; eye-piece No. 3.

Fig. 2.—Fibrinoid metamorphosis of liver cells. To the right are liver cells in various stages of hyaline transformation; to the left the fibrinoid change is shown. Remains of liver cell (?) nuclei may be detected among the fibrils. Methylene blue and eosin staining. Objective No. 6; eye-piece No. 3.

PLATE XII.

Fig. 3.—Focal area of necrosis of liver cells and single cell necroses. Karyolysis to be seen in the centre and pyknosis and karyorhexis in the periphery of the nodule. A few fragments of nuclei are also present in the central portion. Methylene blue and eosin staining. Objective No. 3; eye-piece No. 3.

Fig. 4.—A focal area of necrosis similar to Fig. 3. Magenta staining to show the alterations in nuclei and protoplasm. Karyorhexis is more marked than in preceding figure. Same magnification as preceding figure.

PLATE XIII.

Fig. 5.—Necrosis of single liver cell. Swelling of the protoplasm and fragmentation and metachromatic transformation of the nucleus (karyorhexis). The fragments are retained within the cell protoplasm. Safranin staining. Homogeneous immersion objective $\frac{1}{12}$ in.; eye-piece No. 3.

Fig. 6.—Liver cell with fragmented nucleus (or nuclei?) within the central (intralobular) vein of the liver. Magnification and staining the same as in Fig. 5.

Fig. 7.—Spleen of the rabbit, showing foci of nuclear detritus in the Malpighian body, and great dilatation of the blood spaces of the pulp. The latter contain almost no intact cells, but diffusely scattered cell fragments and small agglomerations of blood pigment. Methylene blue and eosin staining. Objective No. 3; eye-piece No. 3.

PLATE XIV.

Fig. 8.—Phagocyte as seen in the spleen and lymphatic glands. In the latter situation the blood pigment is not constantly present. Safranin staining. Homogeneous immersion objective $\frac{1}{12}$ in.; eye-piece No. 3.

Fig. 9.—Macrophage occupying a large venous sinus in the spleen. The contents are degenerated whole cells, fragments of karyo- and cytoplasm and masses of hæmatoidin pigment. Magenta staining. Homogeneous immersion, objective $\frac{1}{12}$ in.; eye-piece No. 3.

Fig. 10.—Intestinal mucosa, showing several crypts of Lieberkühn. Karyorhexis of epithelial elements and slighter fragmentation of the lymphoid cells without. Magenta staining. Homogeneous immersion, objective $\frac{1}{12}$ in.; eye-piece No. 1.

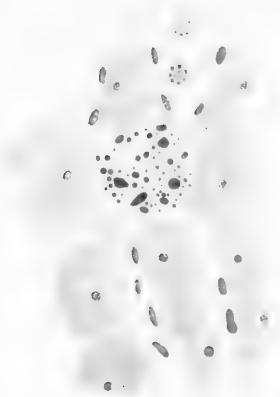

Fig. 5.

Fig. 6.

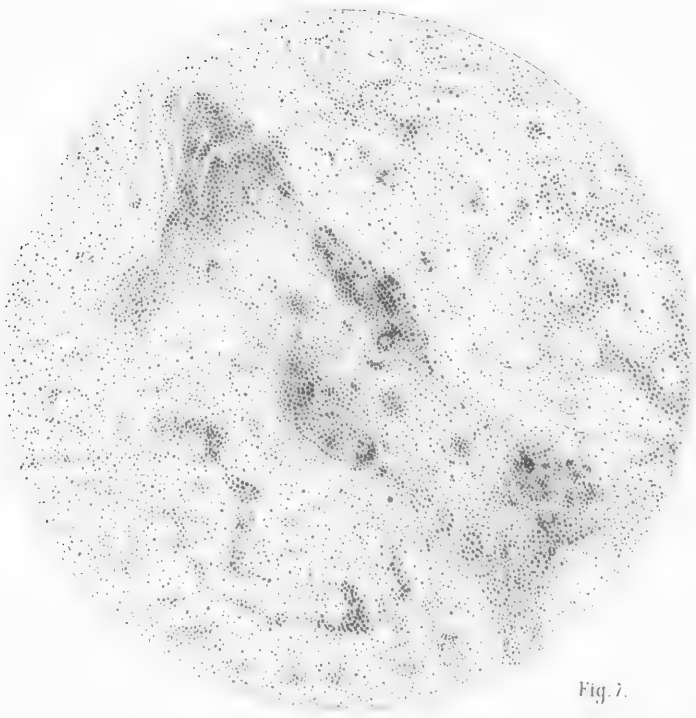

Fig. 7.

Fig. 8.

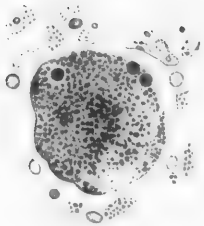

Fig. 9

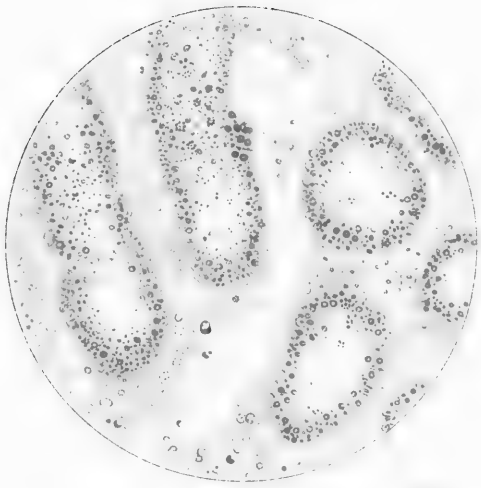

Fig. 10

CHEMISTRY OF COLOSTRUM MILK; A REPORT OF SIX CASES.

By GEORGE WOODWARD, M. D., Associate in Clinical Medicine.
(*From the Pepper Laboratory of Clinical Medicine.*)

That infant-feeding is one of the most promising fields for investigation in the great domain of preventive medicine is a fact becoming more and more appreciated, owing in large measure to the emphasis laid upon it by such writers as Meigs, Rotch and Holt. That good human milk is the ideal food for infants, and that all substitute foods must approach as near as possible to this ideal, are two axioms of pediatrics. The only foundation upon which we can build our substitute food is a knowledge of what good human milk is, *i. e.* of the nature and proportions of its various chemical constituents.

If we dilute cow's milk with water, neutralize and acidify with 0.2 per cent HCl, a flocculent precipitate will fall; this is casein, a nucleo-albumin. If, after filtering, we wash with water and examine the filtrate, we find another albuminous body, distinct from casein and called milk albumin. If we separate this milk albumin by coagulation and filtration, and concentrate the filtrate to a syrup, we find a non-nitrogenous body, crystalline, reducing copper, rotating the plane of polarized light to the right; this is milk sugar. If we now take some fresh milk, shake it with ether, naphtha or rhigolene, decant, evaporate the ether or other substance which has been added, saponify the residue with NaOH, cool, precipitate with HCl, transfer to a filter, wash with water and dissolve with hot alcohol, we have the characteristic penetrating odor of butyric acid. Tributyrin is not the essential fat of milk, triolein and tripalmitin making up more than 90 per cent. But although present in very small amounts, tributyrin proclaims itself, when converted into butyric acid, by its very pungent odor. If we take a third portion of milk, concentrate to a syrup and

burn until no carbon remain, we have the milk salts, or as the residue is usually called, the ash. Such is a rough qualitative analysis of cow's milk.

If we wish to utilize our knowledge of the chemistry of milk in practical medicine, we must know the percentage composition of human milk, which can be determined by quantitative analysis. There are many published analyses to be consulted; but if we compare several of these and note the diversity in the results obtained, we shall conclude that each infant must be a law unto himself and that his best friend is his own mother. This conclusion is well shown by Rotch.*

Among the many analyses showing a wide variety of results, a few only will be selected. J. F. Simon,† as the result of his researches, gives the following table:

Water	82.8
Solids	17.2
Albumin, Casein	4.0
Fat	5.0
Lactose	7.0
Salts	0.31

Tidy,‡ following Simon's methods of analysis, while admitting objections to them, gives somewhat different proportions:

Water	84.07
Solids	15.92
Fat	5.78
Casein	3.22
Lactose	6.51
Salts	0.35

Clemm§ gives the following analysis of the mother's milk for 24 hours after labor:

Water	84.299
Solids	15.701
Salts	0.512

* Pediatrics, pp. 179, 180. Philadelphia, 1895.

† Handbuch der angewandten medizinischen Chemie. Theil ii. Berlin, 1842.

‡ *Clinical Lectures and Reports of the London Hospital*, iv, p. 82. 1867–68.

§ Inquisitiones chemicæ ac microscopicæ in mulierum ac bestiarum complurium lacte. Dissertation, Göttingen, 1845.

For 2 days after birth of child:

Water	86.788
Solids	13.212
Casein	2.182
Albumin	——
Fat	4.863
Lactose	6.099
Salts	——

Mendes de Leon* calculated proteids by taking the difference between the total solids and the sum of the fat, lactose and ash; this remainder he called the albumin and extractives.

E. Pfeiffer† has given us a comprehensive series of analyses showing the daily variations in the percentage composition of mother's milk for an entire year. He, however, used the Ritthausen method of estimating proteids, a method not sufficiently accurate, as has been well shown by Heubner.‡

An objection to all former work is the fact that no precautions in the manner of collecting the milk seem to have been employed. I have also found no reference to the period of nursing when the sample of milk has been taken; in other words, whether the milk examined was "fore," "middle," or "strippings" milk; nowhere does sufficient emphasis seem to have been laid upon absolute cleanliness in the collection of the milk, nor can I find that the necessity of using 24 hours milk was at all appreciated. We know that a trustworthy sample of urine must represent the urine excreted during twenty-four consecutive hours, because there is a decided difference between the morning and evening specimens. I believe, therefore, that on similar grounds a trustworthy sample of milk must represent the milk secreted during twenty-four consecutive hours. For obvious reasons it is not feasible to unite all the milk from all the nursings and use a sample from the total amount secreted in the twenty-four hours. In order to arrive as nearly as possible at this, which would be the ideal method, an especial precaution to be observed is to use only "middle milk." We know that the fore milk and strippings differ widely, and that the

* Ueber die Zusammensetzung der Frauenmilch. Diss. Heidelberg, 1881.
† *Jahrbuch f. Kinderheilkunde*, N. F. xix, 372. 1883.
‡ Ibid., xl, 125. 1895.

middle milk represents very closely the average secretion. To eliminate gross error, therefore, we must avoid the extremes and analyze only the average milk.

When we consult the published analyses we find a notable variation in the percentage of proteids for corresponding periods of lactation. One reason for this is the fact that the proteid percentage does vary within certain limits; a further explanation may be in the fact that some authors use the term proteid as a synonym for casein; lastly, a certain amount of variation undoubtedly arises from the practice of determining the proteid percentage by calculation, in order to avoid the most laborious feature of milk analysis.

In the present paper it is my object to contribute something to our meagre knowledge of human colostrum milk. This milk, secreted for the first few days after parturition, is said to exert a laxative influence upon the infant; the colostrum corpuscles are supposed to disappear in a week or ten days after birth; if they remain, or if they reappear during lactation, they are thought to disturb the infant's digestion; when they have disappeared, the milk is said to be in equilibrium. The corpuscles which characterize colostrum milk are described by A. Czerny* as lymphoid cells, whose office is to take up the unused milk globules, reconstruct them, and finally convey them out of the gland into the lymph channels. In their place appear a considerable number of larger and smaller fat globules, together with which are found small bodies made up of casein and nuclein. The latest analyses of colostrum milk which I can find are those of Harrington,† in which the proteids and lactose percentages are combined, thus rendering the figures unsatisfactory.

The following report embodies the results of analyses of breast milk obtained from the patients of Professor Hirst, and I wish to express to him my appreciation of his courtesy in placing them at my disposal.

METHODS EMPLOYED.

Method of Collection.—The milk was taken from the mother's breasts by means of a breast pump, at stated intervals, from the time

* Festschrift f. Henoch, p. 194. Berlin, 1890.

† Rotch's Pediatrics, p. 167.

of its appearance until it had reached its equilibrium. To obtain the "middle milk" the baby was withdrawn from the breast when it had about half finished nursing, the pump applied, and in this way a certain supply was collected at each nursing for 24 hours; these different portions or samples when mixed formed the 24 hours middle milk which was used for analysis.

Methods of Analysis.—Reaction was obtained by the use of litmus paper, or better, as in later analyses, by the use of an alcoholic solution of rosolic acid.

Specific gravity was obtained by the use of the "areo-picnometer" in distilled water at a temperature of 17.5° C.

Fat was estimated by the Leffmann-Beam method.*

Proteids were estimated by the Kjeldahl method for the determination of nitrogen, as adopted by the Association of Official Agricultural Chemists, September, 1895, the factor 6.38 being employed. A control estimation was made in each case.

Total solids were estimated by drying to constant weight at 110° C. by the Babcock asbestos method.†

Ash was estimated by evaporating to dryness in a weighed platinum dish over a water bath, igniting first over a Bunsen burner and finally with burner and bellows until free from carbon, and subtracting the weight of the dish from the total weight when cool.

Lactose was estimated by adding together the fat, proteids and ash and subtracting the result from the weight of the total solids. In other words, the amount of lactose was obtained by calculation.

RESULTS.

In the following tables the figures all represent weight percentages.

The casein, albumin and globulin are expressed together as "total proteids."

* H. Leffmann and W. Beam. Analysis of Milk and Milk Products, p. 26. Philadelphia, 1893.

† Methods of Analysis, Association of Official Agricultural Chemists U. S. Depart. of Agriculture, Division of Chemistry, p. 36.

Schmidt-Mülheim,* Sebelien† and Johannessen‡ have found in cow's milk nitrogenous bodies other than proteids. Schmidt-Mülheim found urea, lecithin and hypoxanthin, and Sebelien confirmed this observation. Johannessen found kreatin, kreatinin and xanthin bodies. Schmidt-Mülheim and Sebelien estimate the amount of nitrogen from these non-proteid bodies to be from 0.04 to 0.05 per cent, admitting, however, that the limits are by no means constant. Johannessen estimates the nitrogen from these bodies to be 0.025 per cent.

If these non-proteid, nitrogenous bodies be present in human as well as in cow's milk, my proteid percentages must be too high, as they represent all the nitrogen in the milk as proteid nitrogen. In order to gain an idea of my error, I took the first 24 hours colostrum milk and estimated the proteid percentage of the whole milk as usual. With another portion of the milk I proceeded in the following manner: 5 cc. of milk diluted with two volumes of water, a little salt solution added, excess of tannic acid added, the resulting precipitate washed with cold water, and the nitrogen of the precipitate estimated by the Kjeldahl method. A control estimation was made both in the whole milk and the tannic acid precipitate. In the case of the whole milk, the two Kjeldahl estimations showed a difference of 0.00035 gramme of nitrogen; in the case of the tannic acid precipitate, the two Kjeldahl estimations agreed; in the whole milk the proteid percentage was 1.951; in the tannic acid precipitate it was 1.864, a difference of 0.087. In terms of nitrogen, the whole milk gave 0.01575 gramme; the tannic acid precipitate, 0.01505 gramme, a difference of 0.0007 gramme. These results agree with those of Schmidt-Mülheim and Sebelien. They found for every 100 cc. of milk from 40 to 50 milligrammes of nitrogen, due to non-proteid, nitrogenous bodies. In my one examination I found for every 100 cc. of milk 44 milligrammes of such nitrogen. It will be seen from this that the error in my proteid percentages is very slight.

Case I. Sarah S., colored, æt. 23 years, primipara, delivered of female

* Pflüger's *Archiv*, xxx, 379. 1883.
† *Zeitschrift f. physiol. Chemie*, xiii, 135. 1889.
‡ *Jahrbuch f. Kinderheilkunde*, N. F., xxxix, 384. 1894-5.

child, February 7, 7 A. M. Milk appeared February 8. During period of analysis there was an abundant supply of milk, and mother's temperature was never above 99.4° F. Baby weighed at birth 7 lbs.

FIRST 24 HOURS.

Reaction	slightly alkaline
Specific gravity	1030
Fat	3.30%
Total proteids	2.22%
Ash	0.26%
	5.78
Total solids	12.42%
	5.78
Lactose	6.64% (calculated)

Baby weighed 6½ lbs.

SECOND 24 HOURS.

Reaction	alkaline
Gravity	1030
Fat	4%
Proteids	2.02%

This 24 hours milk was defective in amount. Baby weighed 6½ lbs. Colostrum corpuscles found.

THIRD 24 HOURS.

Reaction	alkaline
Gravity	1033
Fat	3.0%
Proteids	2.0%
Ash	0.27%
	5.27
Solids	12.76%
	5.27
Lactose	7.49% (calculated)

Baby weighed 6½ lbs. No colostrum corpuscles to be found. No further analyses undertaken, as the woman developed a high temperature.

Case II. Mary G., æt. 30 years, colored, multipara, delivered of a male child, February 20, 2.30 A. M. Labor and puerperium normal. Lactation established February 21. Baby's weight at birth, 7½ lbs.

FIRST 24 HOURS.

Reaction	alkaline
Gravity	1033
Fat	2.10%
Proteids	2.68%
Ash	0.42%
	5.20
Solids	10.80%
	5.20
Lactose	5.60% (calculated)

Colostrum corpuscles readily found. Baby weighed 7½ lbs.

SECOND 24 HOURS.

Reaction	slightly alkaline
Gravity	1034
Fat	2.00%
Proteids	2.10%
Ash	0.34%
	4.44
Solids	10.18%
	4.44
Lactose	5.74% (calculated)

Colostrum corpuscles found. Baby weighed 7½ lbs.

THIRD 24 HOURS.

Reaction	alkaline
Gravity	1030
Fat	3.10%
Proteids	2.11%
Ash	0.28%
	5.49
Solids	11.55%
	5.49
Lactose	6.06% (calculated)

Colostrum corpuscles found. Baby weighed 7½ lbs.

FOURTH 24 HOURS.

Reaction	alkaline
Gravity	1031
Fat	2.40%

Proteids	1.97%
Ash	0.28%
	4.65
Solids	11.13%
	4.65
Lactose	6.48% (calculated)

Colostrum corpuscles found. Baby weighed 7¾ lbs.

FIFTH 24 HOURS.

Reaction	faintly alkaline
Gravity	1031
Fat	failure
Proteids	1.8%
Ash	0.27%
Solids	11.9%

Colostrum corpuscles found after long search. Baby weighed 7¾ lbs.

Case III. Kate W., æt. 30 years, white, primipara, delivered of male child, 12.35 P. M., March 16, 1896. Puerperium normal. Lactation established March 19. Baby's weight at birth, 7¼ lbs.

FIRST 24 HOURS.

Reaction	alkaline
Gravity	1030
Fat	3.70%
Proteids	1.77%
Ash	0.23%
	5.70
Solids	11.60%
	5.70
Lactose	5.90% (calculated)

No colostrum corpuscles on three slides. Baby weighed 7 lbs.

SECOND 24 HOURS.

Reaction	alkaline
Gravity	1033
Fat	2.80%
Proteids	1.90%
Ash	0.28%
	4.98
Solids	11.98%
	4.98
Lactose	7.00% (calculated)

No colostrum corpuscles found on three slides. Baby weighed 7½ lbs.

THIRD 24 HOURS.

Reaction	faintly alkaline
Gravity	1030
Fat	3.00%
Proteids	1.90%
Ash	0.27%
	5.17
Solids	11.75%
	5.17
Lactose	6.58% (calculated)

No colostrum corpuscles found. Baby weighed 7½ lbs.

FOURTH 24 HOURS.

Gross appearance	watery
Reaction	alkaline
Gravity	1031
Fat	1.80%
Proteids	1.61%
Ash	0.15%
	3.56
Solids	10.82%
	3.56
Lactose	7.26% (calculated)

No colostrum corpuscles found. Baby weighed 7½ lbs. Nurse reported that patient had taken unusually large amounts of water in the preceding 24 hours.

FIFTH 24 HOURS.

Reaction	alkaline
Gravity	1030
Fat	3.10%
Proteids	1.66%
Ash	0.25%
	5.01
Solids	12.07%
	5.01
Lactose	7.06% (calculated)

Baby weighed 7½ lbs.

SIXTH 24 HOURS.

Reaction	alkaline
Gravity	1032
Fat	2.40%

Proteids	1.73%
Ash	0.20%
	4.33
Solids	11.74%
	4.33
Lactose	7.41% (calculated)

Baby weighed 7½ lbs.

SEVENTH 24 HOURS.

Reaction	alkaline
Gravity	1031
Fat	3.60%
Proteids	1.64%
Ash	0.17%
	5.41
Solids	failure

Baby weighed 8 lbs. on day following.

Case IV. Sallie S., æt. 20 years, white, primipara, delivered of male child, May 6th, 7 A. M. Lactation established May 8th. Baby's weight at birth, 7½ lbs.

FIRST 24 HOURS.

Color	yellow
Reaction	alkaline
Gravity	1025
Fat	4.20%
Proteids	1.98%
Ash	0.15%
	6.33
Solids	12.41%
	6.33
Lactose	6.08% (calculated)

Control Kjeldahl differed 0.01 per cent proteid. No colostrum corpuscles found on two slides. Baby weighed 6¾ lbs. Mother's temperature, 6 A. M., normal; 6 P. M., 101° F.

SECOND 24 HOURS.

Reaction	alkaline
Gravity	1025
Fat	4.00%

Proteids	1.69%
Ash	0.15%
	5.84
Solids	12.25%
	5.84
Lactose	6.41% (calculated)

Control Kjeldahl a failure. Baby weighed $6\frac{3}{4}$ lbs.

THIRD 24 HOURS.

Reaction	alkaline
Gravity	1027
Fat	4.25%
Proteids	1.74%
Ash	0.15%
	6.14
Solids	13.11%
	6.14
Lactose	6.97% (calculated)

Control Kjeldahl agreed. Baby weighed $7\frac{1}{2}$ lbs. Mother's temperature, 6 A. M., 100.2° F.; 6 P. M., 100.6° F.

FOURTH 24 HOURS.

Reaction	alkaline
Gravity	1024
Fat	5.00%
Proteids	1.72%
Ash	0.14%
	6.86
Solids	13.82%
	6.86
Lactose	6.96% (calculated)

Control Kjeldahl differed 0.04 per cent proteid or 0.00035 gramme nitrogen; this was due presumably to an accident, the distilling flask having broken after the distillation had progressed for twenty minutes.

Baby weighed 7 lbs. Mother's temperature, 6 A. M., 100° F.; 6 P. M., 103.2° F. On account of the fever, analysis was discontinued.

Case V. Amanda S., æt. 33 years, white, multipara, delivered of female child, October 5, 1896, 9 A. M. Lactation established October 7. Puerperium normal. Baby's weight at birth, $7\frac{1}{2}$ lbs.

FIRST 24 HOURS.

Color	yellow
Reaction	faintly acid (rosolic acid test)
Gravity	1027
Fat	4.00%
Proteids	1.87%
Ash	0.17%
	6.04
Solids	12.00%
	6.04
Lactose	5.96% (calculated)

Control Kjeldahl differed 0.01 per cent proteid. No colostrum corpuscles found. Baby's weight, 7 lbs.

THIRD 24 HOURS.

Color	white
Reaction	acid (rosolic acid test)
Gravity	10285
Fat	3.10%
Proteids	1.89%
Ash	0.15%
	5.14
Solids	11.93%
	5.14
Lactose	6.79% (calculated)

Control Kjeldahl differed 0.04 per cent proteid, or 0.00035 gramme nitrogen. Baby weighed 7½ lbs. No colostrum corpuscles found.

FIFTH 24 HOURS.

Color	white
Reaction	faintly acid (rosolic acid test)
Gravity	1030
Fat	3.00%
Proteids	1.97%
Ash	0.19%
	5.16
Solids	11.90%
	5.16
Lactose	6.74% (calculated)

Control Kjeldahl agreed. No colostrum corpuscles found. Baby weighed 7¾ lbs.

SEVENTH 24 HOURS.

Color	white
Reaction	neutral (rosolic acid test)
Gravity	1031
Fat	4.00%
Proteids	1.97%
Ash	0.097% (loss of ash in manipulation)
	6.067
Solids	12.841%
	6.067
Lactose	6.774% (calculated)

Control Kjeldahl differed 0.01 per cent proteid. Baby weighed 8 lbs.

Case VI. Clara M., æt. 18 years, white, primipara, delivered of male child, November 16, 1896, 7 A. M. Lactation established November 18. Puerperium normal. Baby's weight at birth, 6¼ lbs.

FIRST 24 HOURS.

Color	yellow-white
Reaction	slightly alkaline (rosolic test)
Gravity	1029
Fat	4.00%
Proteids	2.06%
Ash	0.19%
	6.25
Solids	12.38%
	6.25
Lactose	6.13% (calculated)

Control Kjeldahl differed 0.01 per cent proteid. Colostrum corpuscles very easily demonstrated after centrifugation.* Baby weighed 5¾ lbs.

THIRD 24 HOURS.

Color	yellowish white
Reaction	faintly alkaline (rosolic test)
Gravity	1031
Fat	5.30%

* At the suggestion of Dr. Alfred Stengel, Director of the Pepper Laboratory, I tried centrifugation at moderate speed to aid in the detection of the colostrum corpuscles.

Proteids	1.94%
Ash	0.19%
	7.43
Solids	13.65%
	7.43
Lactose	6.22% (calculated)

Control Kjeldahl agreed. Colostrum corpuscles found with difficulty after centrifugation. Baby weighed 6 lbs.

FIFTH 24 HOURS.

Color	white
Reaction	alkaline (rosolic test)
Gravity	1028
Fat	5.00%
Proteids	1.78%
Ash	0.21%
	6.99
Solids	13.06%
	6.99
Lactose	6.07% (calculated)

Control Kjeldahl differed 0.08 per cent proteid. No colostrum corpuscles found after centrifugation. Baby weighed 6⅜ lbs.

CONCLUSIONS.

Colostrum corpuscles are not always found in so-called colostrum milk; when they are present, the percentage of proteids is higher;* as they disappear, the proteid percentage drops.

The color of colostrum milk is yellow; this color is especially marked in negroes' milk (observed in four cases not included in this report).

The reaction of colostrum milk is alkaline.

The specific gravity varies from 1024 to 1034. This variation is chiefly due to the variation in the amount of fat present.

* Two cases not included in this report strengthen this conclusion:

I. M. B., æt. 22, white, primipara, delivered of male child; colostrum corpuscles found very easily without centrifugation; proteids 2.4%.

II. Multipara, æt. 23, half negro and half Indian; no colostrum corpuscles found after diligent search, both without and with centrifugation; proteids 1.5%.

The fat varies from 2 per cent (disregarding the fourth 24 hours of Case III as being abnormal) to 5.3 per cent.

The proteids vary from 1.64 per cent (disregarding again Case III as abnormal) to 2.22 per cent.

The ash varies from 0.14 per cent to 0.42 per cent. The higher percentages of ash in the earlier analyses are probably incorrect, a result due to imperfect ignition.

The total solids vary from 10.18 per cent to 13.65 per cent.

The lactose (calculated) varies from 5.6 per cent to 7.4 per cent.

An average colostrum milk contains 4 per cent of fat, 1.9 per cent of proteids, 6.5 per cent of lactose, 0.2 per cent of ash, making the total solids 12.5 per cent and water 87.5 per cent.

Cases II and V agree with the observations of Townsend,* that the infants of multiparæ do not lose as much weight in the colostrum period of lactation as the children of primiparæ.

Cases I, III, V and VI show results which agree with those of the same observer, that the shorter the period of colostrum milk, the smaller is the so-called physiological loss of weight in the new-born.

Case I, in which colostrum corpuscles were found, and Case IV, in which these corpuscles were not found, but in both of which high temperatures developed, show losses of infant weight of 8 and 12 ounces respectively.

The following report has been kindly made for me by Dr. A. E. Taylor, Associate in Clinical Medicine, Pepper Clinical Laboratory:

Microscopic Examination of Colostrum Corpuscles.—Fixed and stained, the corpuscles are smaller than they appear in the freshly spread specimens, measuring from 12 to 22 μ in diameter. They have a small, irregular, but much degenerated nucleus. The protoplasm is more or less filled with large and small granules, only a few of which are stained by osmic acid. These granules refuse staining with acid, basic and neutral dyes; they show the characteristics of proteids in their reactions. The few granules which are stained by osmic acid are probably fatty. The most marked feature is the constant and extensive degeneration.

* Roteh's Pediatrics, p. 100.